December 2005 Issue | T. Colin Campbell, PhD Jacob Gould Schurman, Professor Emeritus of Nutritional Chemistry

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Welcome to *Functional Medicine Update* for December 2005. This has been quite a year in functional medicine. We have had an opportunity to explore and share some extraordinary ideas from the experiences and thoughts of leaders in our field. Most interestingly, as we move into 2006, we are leaving behind a very important legacy for the future development of functional medicine—its first textbook, published by The Institute for Functional Medicine. I could not be more proud of the dedicated individuals who collaborated on this project—Sheila Quinn, Senior Editor, and Dr. David Jones, President of IFM. They have worked extraordinarily hard on the development of this textbook, which will be published this month. I believe you will find this book immensely valuable. To coin a phrase, it provides "news to use." It contains important information from which strategies can be developed for personalizing patient interventions across a wide range of chronic diseases. It will help thoughtful clinicians to significantly improve patient outcomes. It contains over 800 pages and thousands of references, with 47 authors from many disciplines, all working toward a central theme. It has undergone blinded review by independent experts, is consistent in style and readability, and is a testament to the evolution of this field over the last 20 years. If you have not yet had a chance to see a copy of this book, I strongly recommend it. It will help guide you in ways to properly use functional medicine concepts in clinical practice.

I also want to remind you that the 13th International Symposium on Functional Medicine will be coming up April 19-22, 2006 (a little earlier this year) at the Tampa Marriott Waterside Hotel & Marina in Tampa, Florida. One of the keynote plenary presenters is going to be this month's Clinician/Researcher of the Month—Dr. T. Colin Campbell. We will be focusing on detoxification and biotransformation at the symposium. Please mark the dates on your calendar. This is going to be a very auspicious event, with superb speakers, informative plenary lectures and workshops, and an excellent overall meeting format.

In this month's FMU, I am going to focus on one of the themes that will be explored at the 13th International Symposium on Functional Medicine having to do with the question of whether or not our present diet is toxic. Just to pose that question will raise some fairly strong comments. What do I mean by "present diet?" What do I mean by "toxic?" Before these questions can be answered, we must first understand the definitions of the terms.

The diet I am talking about is one of standard fare. It is highly processed, shelf-stable, convenient, reasonably inexpensive, and is available to virtually everyone across the United States. We have been characterized as the "fast-food nation," with a diet of "white," of over-consumption, and of under-nutrition. Whatever that means to you, it is probably the diet that most of your patients are eating, no

matter what they are telling you. Over time, they have probably been consuming foods that are represented by those characteristics as the majority of their calories —shelf stable, "white," high in fat, high in sugar, and highly refined.

Let me move to the next definition. What does "toxic" mean? Toxic refers to some metabolic influence of the exposure that induces activities in the complex web of metabolomic interaction leading to tissue injury. As contrasted to a poison that might have an acute toxicity, I am referring to chronic toxicity where, over time, the appearance of specific metabolites that would not normally be present in a healthy physiology, eventually induce injury to tissues, producing a chronic, cumulative influence that is likely to lead to degenerative disease. That disease might evolve over decades of living before it is finally observed. Therefore, it is hard to pin down a specific etiology agent for it because it evolves so slowly. It is like the Chinese water torture of one drop of water at a time on one's forehead. Each drop in itself is not a major problem, but it is likely that years of single drops will create a significant problem.

The term "diet toxicity" sounds exaggerated, but the outcome is exactly what the term implies. People get diseases prematurely that are not necessarily preordained, and for which heroic medical intervention is required at great expense and often discomfort to the patient with some relative risk. The term "toxicity," as I am applying it in this month's FMU, may not be the traditional terminology a toxicologist would use, but I believe it will fulfill our definition of toxicity. Once again, I will pose the question—is today's standard diet toxic? The outcome of a toxic diet would be the major chronic age-related diseases—coronary artery disease, cerebrovascular disease, hypertension-related disorders, cancer of various forms, digestive disorders, and various other inflammatory conditions.

It is interesting to ask why esophageal reflux disorder, or GERD, is becoming so prevalent. It is almost as if everyone has to take an appropriate H2 blocker, proton pump inhibitor, or antacid so they can cope with normal daily living. Why? Why is it that we are seeing such a steep increase in upper GI-related disorders, and assuming it is OK because we have all these new drugs to keep people's gastric juices and esophageal function under control? One has to ask what the cause is, rather than just what the effect is.

I want to focus the rest of this issue on a measurable implication of a toxic diet, and that is the epidemic of metabolic syndrome. The debate is no longer about the prevalence of metabolic syndrome and what its diagnostic criteria are; these are now well established. But defining metabolic syndrome in such a way that it sounds like a discrete pathology that is either present or absent results in apparently reducing the number of people who are affected by underlying insulin resistance and, potentially trivializing that condition until people start showing up with premature heart attacks and strokes, and wondering where they originated. We will have medicalization of those conditions with new stenting, new bypass surgeries, and new medications, but, we will not have asked the right questions, early enough, however, about the relative toxicity of the diet and its relationship to the incipient markers of later-stage vascular dysfunction, which is one possible outcome of metabolic syndrome.

What is metabolic syndrome? According to Eckel, Grundy, and Zimmet, in an article published in the *Lancet:* "The metabolic syndrome is a common metabolic disorder that results from the increasing prevalence of obesity."[1] There are many people, including Dr. Reaven, who might challenge that metabolic syndrome is simply a result of obesity, although he agrees that it is a factor. Metabolic syndrome also appears to have genetic factors, as well as other lifestyle factors, such as amount of exercise, involved in its etiology. It is not obesity or its covariables alone that cause metabolic syndrome,

at least in all people with the syndrome. If that were the case, how could we explain the individual who is very thin who has metabolic syndrome and insulin resistance? There are cases of people with low body weight, who are perhaps excessively lean, that have metabolic syndrome, as well. It is not obesity alone that causes metabolic syndrome.

Metabolic syndrome is defined in various ways, but generally, an individual with this condition has slightly elevated fasting triglycerides and slightly lowered HDL levels, increased blood pressure (at least, marginal elevations of systolic pressure), and often elevated blood uric acid levels. They generally have central obesity, as we mentioned, with increased waist-to-hip ratios and an elevated body mass index (BMI). They often have elevated dense LDL particles. None of those by itself is the sine qua non for metabolic syndrome. A constellation of variables is associated with the diagnostic markers of metabolic syndrome.

The principal diagnostic marker would be found by doing an insulin clamp study on an individual, the so-called euglycemic clamp, when insulin and glucose are infused to evaluate the relative sensitivity of that person to the infusion. That is not a technique that is going to be routinely used in diagnosis, so the surrogate markers are used, such as triglyceride over HDL ratio, or various types of homeostasis models for glycemic or insulin response.

Inflammation as a Marker of Metabolic Syndrome
Another hallmark of metabolic syndrome is inflammation. This is a more recent emerging concept—that the pathophysiology of metabolic syndrome seems to be largely attributable to insulin resistance, with excessive flux of fatty acids through the liver inducing or associated with a proinflammatory state reflecting increased levels of proinflammatory cytokines and eicosanoids. The increased risk for vascular injury, endothelial injury, hypertensive dysfunction, renal problems, and cerebral vascular problems associated with metabolic syndrome, may be a consequence of the metabolic markers or mediators of inflammation.

Obesity and Inflammation
Central obesity, or visceral adipose tissue, produces its own complex array of proinflammatory molecules, such as tumor necrosis factor alpha (TNF-α), interleukin 1 (IL-1), and interleukin 6 (IL-6). These messenger molecules also add to the production of proinflammatory signals, along with activated macrophages and an inflamed vascular endothelium. When a person has an occlusion, these are all sites or loci in the body where there is increased production of proinflammatory mediators. These mediators are also associated with the metabolic syndrome.

There is also some evidence that the pathophysiology of metabolic syndrome may actually begin in the perinatal period. Often, we start thinking about a chronic, age-related, degenerative disease when the person becomes middle-aged, and then we become worried about it. Yet, the origin of many of these disorders may have occurred *in utero*. There is a sequel of events that may have started the moment the sperm met the egg in the uterine environment that travels *post utero* into the infant period, the toddler period, and later into adolescence and adulthood.

Let me give you an example from a paper that was published in the journal, *Nutrition*,titled "Pathophysiology of metabolic syndrome X and its links to the perinatal period." [2] In this paper, the author states:

"Increased consumption of energy-dense diets by pregnant women and lactating mothers suppresses the activities of Δ-6 and Δ-5 desaturases not only in maternal tissues but also in fetal liver and the placenta, resulting in decreased plasma and tissue concentrations of long-chain polyunsaturated fatty acids ω-6 arachidonic acid (AA), ω-3 eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA)."

We know of the importance of DHA in the infant for ocular and neurological development.

"EPA, DHA, and AA have negative feedback control on tumor necrosis factor-α and IL-6 synthesis. Hence, EPA, DHA, and AA deficiencies induced by an energy-dense diet increase generation of tumor necrosis factor-α and interleukin-6, markers of inflammation that in turn decrease production of endothelial nitric oxide and adiponectin to induce insulin resistance in maternal and fetal tissues."

In fact, insulin resistance can be induced in animals by infusing very small amounts of TNF-αor IL-6, or even prostaglandin-E2 (PGE-2). PGE-2 can induce insulin resistance. There is a fairly close correlation between inflammation and insulin resistance, regardless of BMI principles.

"Increased concentration of tumor necrosis factor-α and interleukin-6 enhance expression and activity of 11β-hydroxysteroid dehydrogenase type 1 enzyme, which produces abdominal obesity, insulin resistance, hyperlipidemia, hyperphagia, and hyperleptinemia, characteristic features of metabolic syndrome X."

11β-hydroxysteroid dehydrogenase type 1 produces regional cortisol. One thing we know about people with metabolic syndrome is that often their body changes into the apple shape, with an increased waist-to-hip ratio that seems to resemble a physiognomy like that of Cushing's disorder. They do not have a primary, adrenal hyperplasia, however. There is something else going on, which is regional cortisol production induced by adipocyte activation of 11β-hydroxysteroid dehydrogenase type 1, which is induced in its gene expression by exposure to the proinflammatory Th-1-inducing cytokines, such as TNF-α and IL-6. If there is an upregulation of inflammation in the maternal diet and environment, there is stimulation in the fetal liver and in the adipocyte for production of these genes, or activation of the expression of these genes, associated with regional production of cortisol and other metabolic effects.

The takeaway from this discussion is that during pregnancy, lowering the load of proinflammatory materials in the diet and increasing the level of long-chain polyunsaturated fatty acids, particularly EPA and DHA, may be very desirable during the perinatal period in preventing ultimate development of metabolic syndrome through the gene-activation processes. Of course, that model holds true, not just *in utero*, but *post utero*, as well.

It also raises the implication that one of the surrogate markers for the assessment of the metabolic syndrome is not only triglyceride/HDL ratios above 4, but also evaluation of various inflammatory mediators, including high-sensitivity C-reactive protein (hsCRP). There was a nice report in *Clinical Chemistry* looking at the relationship between CRP levels and cardiovascular event survival probability.[3] It has been found that as CRP goes from less than 1 mg per liter to 1-3 mg per liter to greater than 3 mg per liter, the incidence of cardiovascular events goes up remarkably. The Kaplan Meier survival curves of those events were pretty dramatic, demonstrating that keeping hsCRP at a level less than 1 is pretty important. It is a push/pull, chicken-and-egg argument. It is all part of the web. Insulin resistance induces oxidative stress and inflammation, and around it goes in a feed-forward cycle.

One of the agents in the diet that has been associated with the production of inflammatory, insulin resistance responses is the simple carbohydrate, fructose. There has been a considerable increase of fructose in the diet as we moved from cane and beet sugar to that of corn-derived sweeteners, the high-fructose corn syrup sweeteners. Fructose intake has been associated with the prevalence of obesity, as well as hepatic lipogenesis and hyperlipidemia. Although it does not increase insulin and leptin, or suppress ghrelin (which suggests that it has a different effect than glucose on energy balance through an endocrine mechanism), it may have an increased tendency, if consumed at high levels (high is dependent on the eye of the observer), to induce hypertriglyceridemia and an altered effect on the triglyceride/HDL ratio, which we have already said is associated with metabolic syndrome.

In an article on dietary fructose that appeared in *Nutrition Reviews*, titled "Dietary fructose: implications for dysregulation of energy homeostasis and lipid/carbohydrate metabolism,"the author, Peter Havel (whose name is familiar to those of us in nutrition circles), discusses that chronic hyperinsulinemia relates to hepatic lipogenesis and may contribute to hypertriglyceridemia.[6] This has been seen in animals and in humans in some limited trials with excessive fructose intake. The rodent model is the animal on whom many of these studies have been done, and it turns out they are very sensitive to fructose in the diet. They can be induced into hypertriglyceridemia quite easily with increased levels of fructose in the diet. Human metabolism of fructose, however, differs from that of rodents, and the ability to produce simple hypertriglyceridemia with increased fructose is not as obvious. However, there is a level, a threshold at which, in certain individuals, excessive intake, particularly as corn syrup-sweetened beverages, induces hypertriglyceridemia and may be associated with one of the etiological factors implicated in metabolic syndrome and insulin resistance. The connection between fructose and insulin resistance is not a trivial one.

In a paper that appeared in *Diabetes*, investigators conducted a human study looking at high-fructose diets that stimulated hepatic *de novo* lipogenesis and caused hypertriglyceridemia and insulin resistance.[7] Seven apparently normal men were studied on four occasions: after fish oil supplements of 7.2 grams per day for 28 days; after a six-day, high-fructose diet corresponding to an extra 25 percent of calories; after a fish oil plus high-fructose diet; and after a control diet. Following each condition, fasting fractional levels of *de novo* lipogenesis and glucose production were evaluated using 1-^{13}C sodium acetate uptake and 6,6-$^{2}H_2$glucose into various fractions of lipids. It is a very nice study. I want to emphasize that increasing fructose intake to constitute 3 grams fructose per kg body weight did induce dyslipidemia and hepatic and adipose tissue insulin resistance, whereas the 7.5 grams per day of fish oil reversed dyslipidemia but not insulin resistance.

A lot of people have jumped on the bandwagon who believe that fructose causes metabolic syndrome and insulin resistance. But again, I want to say, everything in balance. According to Tolman's Law of Pharmacology, everything is toxic at some level, including air and water. The real question is, at what level does fructose become "lipid toxic" or hepatotoxic? It appears that is when fructose is upward of 25 percent or more of calories. Let's assume, just for math purposes, that the person was consuming a 1600 calorie-a-day diet. Twenty-five percent is 400 of those 1600 calories. If we talk about it as 4 calories per gram, that's 100 grams or more of fructose that a person would have to be consuming to get up to that level. One hundred grams of fructose, or more, is a very high load. About the only time you will see that is if a person is on a high-sweet diet and consuming high fructose corn-syrup sweetened beverages. Yes, fructose is hypertriglyceridemic, and yes, it can induce insulin resistance in humans, but the amount needed to document the effect is very high.

We have talked about the toxic dietary components of high fat, highsugar, and white flour. What about the converse? Can one formulate a diet regime with low toxicity? That leads into studies like those that have discussed the effect of a Mediterranean-style diet on endothelial function, and markers of vascular inflammation in patients with metabolic syndrome. There was a nice paper published in the *Journal of the American Medical Association* in which the authors conducted a human intervention trial with 90 subjects who were instructed to follow a Mediterranean-style diet. They received detailed advice as to how to increase daily consumption of whole grains, fruits, vegetables, nuts, and olive oil.[8] Another 90 patients in the control group followed a prudent diet, which consisted of 50 to 60 percent of calories as carbohydrate (not specifying unrefined, necessarily), protein level 15-20 percent of calories, and total fat less than 30 percent of calories. It was comparable to the American Heart Association's Step 1 Diet. After two years, patients following the Mediterranean-style diet consumed more foods rich in monounsaturated fat, polyunsaturated fat, and fiber, had a lower ratio of omega-6 to omega-3 fatty acids. Obviously, their total fruit, vegetable, and nut intake (about 270 grams a day), and whole-grain intake (about 103 grams a day), was also significantly higher than the control group. The level of physical activity in both groups was about the same, and the outcome was quite dramatic. At two years of follow-up, the patients in the Mediterranean diet group had significantly improved insulin sensitivity and reduced serum concentrations of hsCRP and IL-6. There were many individuals who had metabolic syndrome both study groups (40 of 90 in the Mediterranean-style diet group, versus 78 of 90 in the control group). It was concluded that the Mediterranean-style diet may be effective in reducing the prevalence of metabolic syndrome and its associated cardiovascular risk.

That follows on with a paper by David Jenkins, et al, from the University of Toronto School of Medicine, Department of Nutrition, published in the *American Journal of Clinical Nutrition,*and a classic study that I have referred to in the past. The title is, "A direct comparison of a dietary portfolio of cholesterol-lowering foods with a statin in hypercholesterolemic participants."[9] These were individuals who did not have heart disease or diabetes, but who did have a history of elevated lipids. There were 34 hyperlipidemic participants—20 men and 14 postmenopausal women. They all completed three different treatments with a washout between each: a control diet group on the AHA's Step 1 diet; a diet very rich in plant sterols, soy protein, and various viscous fibers; and the AHA's Step 1 diet, along with a statin (Lovastatin). It was found that in the AHA Step 1 diet group, the diet did not have a very positive effect on inflammation or insulin markers, but the group on the portfolio of cholesterol-lowering foods (2000 mg per day of phytosterols rich in beta sistosterol, along with soy protein and the higher soluble fiber) had a very marked reduction in triglycerides, improvement in insulin sensitivity, and a lowered level of inflammatory mediators.

As Dr. Jenkins and his colleagues point out, dietary combinations may not differ in calories, or even in macronutrient percent calories, but they may differ significantly in their impact on metabolic outcome. In fact, when this dietary portfolio of cholesterol-lowering foods was compared with one of statins and an AHA Step 1 diet, both regimens were about the same regarding the ability to lower lipids and improve function. One might ask what a toxic diet is, because it might suggest that even the AHA Step 1 Diet has some residual toxicity. If it was an optimal diet, you would not see the improvements observed with the cholesterol-lowering foods (the plant sterol-rich, soy protein-rich, higher viscous rich fiber diet), which had a much lower glycemic index.

I mentioned soy, and probably I should talk a bit about the soy connection to cognitive function. Recently, a study from the Psychopharmacology Research Unit, Centre for Neuroscience, King's College

London at the Guy's Campus in London and the School of Pharmacy in Brunswick Square in London, titled "Soya administration and cognitive function in post-menopausal women" was published.[10] The authors of this paper in *Current Topics in Nutraceutical Research* conclude that, under more controlled conditions, inclusion of soy in the diet has a positive effect on cognitive function in postmenopausal women.

The other feature that we have not talked about in any of this work, which I think deserves attention, is what happens when you refine a diet very rich in plant phytochemicals and phytonutrients, into a "white" diet, and you make it a diet rich in calories, but low in associated nutrients? This change fuels the overconsumptive/-undernutrition state. This is the diet that we have defined as toxic, which delivers a lot of potential energy in the way of calories, but not the right kind of supporting players in order for those calories to be properly metabolized.

Historically, we have eaten diets somewhere in between vegetarian and carnivore, because we have the incisors of the carnivore and the molars, or grinding teeth, of the herbivores. When we eat these types of varied diets we are not just getting protein, carbohydrate, and fat alone. We are getting non-digestible fibers, and literally tens of thousands of phytochemicals in the coloring materials of those foods—pigments, phenols, glycosides, flavonoids, and so forth.

What effect do these natural phytochemicals have on insulin sensitivity, and on cellular signalling and function? This question is only now being seriously addressed. In the past, we thought we could remove these non-nutritive items. They were not vitamins and they were not minerals, so we could just take them out of food and do our studies with animals, and it would be the same as if they were still included, because they were considered benign. Now, we recognize that is not true. These phytochemicals can have unique, tissue-specific effects on function. If we want to know what the role of a complex diet is in modulating genomic expression, proteomics, and metabolomics into the phenomics of the organism, we need to look at the role that phytochemicals have on function, as well. This is an opportunity to do new, detailed research, and as this research is done, we will uncover the fact that vegetable diets (by nature, the only diets that can contain phytochemicals) have a different effect than that of highly processed diets, or diets rich in only animal products.

This is, in part, what Mark McCarty talks about in his hypothesis article in *Medical Hypotheses*, titled "Potential utility of natural polyphenols for reversing fat-induced insulin resistance."[11] Eating a complex diet with all these phytochemicals influences gene expression, proteomic, and metabolomic function, and can have a salutory effect on the way calories are processed into functional energy. This is a very important point of differentiation between the partially refined diet and the highly refined, nutrient-dense diet that may stimulate a toxic outcome.

It is time for our Clinician/Researcher of the Month.

INTERVIEW TRANSCRIPT

T. Colin Campbell, PhD
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JB: During our ongoing paradigm shift, we have been very fortunate to hear from some of the great minds in this field. This month is no exception. We are privileged to have Dr. T. Colin Campbell, a name that I'm sure is familiar to many of you. He has been a leader in our field for many years. He is the Jacob Gould Schurman Professor Emeritus of Nutritional Biochemistry at Cornell University, and the project director of the China-Oxford-Cornell Diet and Health Project. This study was the culmination of a 20-year partnership of Cornell University, Oxford University, and the Chinese Academy of Preventive Medicine. Dr. Campbell also has a rich and impressive publication list. It's wonderful to have the opportunity to share in his wisdom, background, and history. His graduate training took place in the late 1950s, and what has happened since that time in the areas of nutritional science, genomics, nutrigenomics, epidemiology, animal science, and all of the aspects of human biochemistry that we didn't yet know back then, is quite amazing. Dr. Campbell has helped to shepherd that, and he has been present through this whole revolution.

I thought it might be useful for Dr. Campbell to share his historical perspective, as well as some of the extraordinary things he describes in his landmark book (one that should be in all of our libraries)—The China Study.12 This represents the largest health and nutrition study ever conducted. Some people call it the "Charles Darwin work of nutrition." If you haven't read this book, you certainly should put it on your reading list. It opens up tremendous opportunities for understanding the revolution we are now engaged in, and the implications and importance it has in global health and stemming the tide of the ever-rising burden of chronic, age-related disease.

Welcome to FMU, Dr. Campbell. As I read your original research articles, I found it fascinating to see how your intellectual stream of thinking may have started what the embryonic ideas were, and how it related to some of the observations you made about dietary protein, detoxification, and hepatocarcinogenesis. How did you get into this field and make those first observations?

Protein in the Diets of Malnourished Children in the Philippines

TC: I want to thank you for your invitation and for all of those kind comments. I started on a dairy farm, and went off to school to do my doctoral dissertation on trying to figure out how to produce animal protein more efficiently for consumption. I went to the Philippines to set up a nationwide program to feed malnourished children. One of the objectives, not just for me, but for all those working in the field at that time, was to make sure the children got enough protein. Along the way, as sort of a side observation, I learned that there were kids there getting primary liver cancer at age 4 and under, which is very unusual. That disease tends to occur in mid- to older-age. I learned that the kids who were consuming the most protein tended to come from families who were consuming a western diet. We were trying to push more protein, in a sense; yet those who were getting the highest levels of protein were having problems, and possibly getting liver cancer, as well as other types of cancer.

Animal Study on Protein and Liver Cancer

At that time, there was an experimental animal study done in India, that showed esssentially the same thing. When rats were given aflatoxin, which is a very potent hepatocarcinogen, it caused liver cancer. When the rats were given either regular levels of protein at 20 percent of calories, compared with other rats given protein at 5 percent of calories thinking that the animals given more protein would be at an advantage, in terms of resistance to aflatoxin—in fact, the reverse turned out to be the case. The results

were remarkable. It wasn't necessary to have a statistician on board to see whether or not it was significant. It was essentially like a 100 percent score. The rats who got the most protein got liver cancer, and the rats who got the least amount of protein did not, and that was consistent with what I had seen in the kids. It was just putting one and one together, and not only getting two, but maybe more.

Protein and Metabolism of Aflatoxin

I embarked on a long series of studies that were funded, for the most part, by the National Institutes of Health (NIH) and, to some extent, by the American Cancer Society and the American Institute for Cancer Research. It was all public money. We explored that question, starting out to confirm the observation that higher levels of protein could turn on that tumor. The second question was to try to figure out how it worked. In the field of science, if we know how something works, we have a lot of confidence in what we're seeing. We had a continuous NIH grant to work on that for about 19 years. We looked at it in great depth. We first wanted to know whether the protein affected the metabolism of aflatoxin by the so-called drug metabolism enzyme system. And, indeed, it did. And it was remarkable—very strong. Higher protein increased the enzymatic activation of aflatoxin to produce an electrophilic reactive metabolite that covalently bound to DNA. We were at the forefront, in a way, even though we didn't have a lot of tools to work with. In any case, higher protein levels increased the activation of the aflatoxin to form more of these DNA adducts which, in turn, represented intiation of a lesion. It seemed as if every time we looked for a mechanism, we found one, which was another observation in itself, and kind of exciting. It wasn't just a single mechanism; it was a whole bunch of changes in enzyme activities and other sorts of physiological biochemical events that converged to create that response. We went beyond that to look at the question concerning the infective protein promotion. We knew in those days that promotion seemed to be a reversible process of the cancer initiation. I knew that higher protein intake increased the activation of aflatoxin, but all that might be cancelled out if, in fact, it didn't do the same thing during promotion. We looked at that and found that the higher protein levels actually increased promotion, as well. It grew the tumors essentially. It was acting a bit like fertilizer, growing the grass faster; in this case, growing the tumor faster. We also learned that multiple mechanisms operating in an almost symphonic manner were working to produce that result. At the same time, we learned that whereas we could move the tumor forward in its progress by feeding higher protein, we could also reverse the process by feeding lower protein. That was an exciting observation.

Plant versus Animal Protein

Probably, the next most significant thing we observed was that the protein we were using was casein, or animal protein. We tried some plant proteins, like wheat and soy protein, and they did not promote tumor development. That was very clear and very distinctly different, although I stated that in quite simplistic terms. We were focusing on the idea that we had an animal protein on the one hand that promoted tumors, and plant proteins that did not. I thought that was quite striking. It was in-depth as far as the details were concerned, but we didn't explore the protein, so it was limited in that sense. We eventually got involved in doing a survey in China, a human, nationwide study, to see why cancer occurred in some places in the country much more commonly than in other places. The Chinese Government had established that cancer rates were highly localized across the country. Together, with colleagues from the University of Oxford and the College of China, and some others, we organized this big study in China, a large cooperative study funded by the NIH and the Chinese Government. We wanted to measure as many things as we possibly could because I had suddenly become interested in looking at the question concerning the relationship between diet and disease in a much more comprehensive manner, rather than focusing on one thing at a time. The rat studies we had done were interesting and informative, but I wanted to go beyond

that and look at things in a larger context.

The China Study

I guess the rest is history. In the China study, in rural China at least, they don't consume much in the way of animal foods. It goes from something in some areas, to almost nothing, to perhaps 20 percent of calories in other areas. We were looking at that end of the curve where not much animal food was consumed. I didn't think that we would see a whole lot. We measured things in so many different ways—we took blood and urine samples, food samples, asked questions, and analyzed the responses for all manner of things. It gave us an opportunity to look at the question of the relationship of diet and lifestyle with disease formation in a much more comprehensive way. What we came away with was quite startling. It confirmed the impressions that I had from the animal studies—mainly, that putting some animal food in the diet wasn't a very good idea. The consequences were more than just creating more cancer; they were also associated with creating more heart disease, more diabetes, and more this and more that—the kinds of conditions we get here in the western countries. Conversely, whole plant foods—vegetables, fruits, grains—seem to have this very exciting property of keeping these diseases at bay. They even reversed these diseases. It was a combination of the experimental animal studies and the human studies, together with an emerging literature on the part of many other laboratories, as well.

The whole story started to gel into a thesis for me—that here in the west, we're not doing things the right way. We're consuming a diet that is causing problems across the board, one that is very rich in animal-based foods, for starters, and also a diet that is very limited in whole, plant-based foods. To the extent that we use plant-based constituents, we usually end up extracting the stuff out of the plants, making junk food, and eating that at convenience stores. We've got a diet of rich, fatty animal foods, together with junk food, and leaving out the best parts. The result is that we are getting ourselves into some serious trouble.

As one does research and goes through the years, one may make a discovery, after which one moves on to the next thing. But I have developed a great passion for the idea that nutrition ought to be the premier biomedical science for the future. There's no doubt in my mind about that. I've also become aware that the public is very confused about what nutrition really does. Our professional colleagues are confused. I think your institute, by the way, has got the right name—Institute for Functional Medicine. I'm sure you focus a great deal on food. That is the way of the future; there's no question about that. It seems to me that it's more of a question of stopping long enough in research and the practice of medicine to deliberate on this idea. It's not simple; it's complex biologically, but we can begin to understand the process and become aware of how profound its effect is. I've gotten to the point where I believe that a plant-based diet with lots of variety is the ideal. That diet works in so many exciting ways. It keeps mischievious genes under control; there's a lot of good evidence showing that. We did some of that ourselves. To a considerable extent, it attenuates the effects of toxic agents we are exposed to. It reverses advanced diseases. The same diet that prevents disease tends to also be useful in treating people with diseases far along, and we can see reversal.

JB: I'm awestruck. I'm sure all of our listeners are. Because what you speak of so easily and so fluently is a manifesto for change. It translates from academia and the research to the lives of people, suffering, and premature loss of human potential. There are many sociological, philosophical, and humanitarian implications of what you're saying. That's one of the reasons I was drawn to the Pauling Insitute, where I worked for Dr. Linus Pauling for three years. There are some bigger issues that derive out of this science than just the discoveries, one of which is the implication on people's lives throughout the world. I'd like to go back and pick up several things you said. Perhaps the profundity was not fully appreciated by some of

our listeners.

Let me start with the presumption of a scientist. Often, we feel that scientific investigators are a product of their own bias and their own environment, but great scientists are those that can shake off their bias and see the world in a different way. I'm reminded of the Goldbergers when they discovered that pellagra resulted from niacin deficiency. They were bacteriologists and were sent to find the infectious organism that caused pellagra. In the process, they were able to see through their own bias.

Similarly, you are a product of a dairy farm. You must have had to fight off your presumptions, because I'm sure you grew up on those great farm breakfasts. Was that a complicated transition as you began to make these discoveries?

TC: Yes, it was. It was very complex. One advantage for me is that I remained the skeptic of our own research as it began to unfold. I was probably a severe skeptic, which made me look harder to really prove true what we were looking at, and my colleagues did the same along the way, as well. Although we were generously funded for many years by NIH, most of the proposals and arguments that were made at that time were focused more on how cancer works. We were using protein as a model to explore that process. But, as I started to focus more on the agent itself, namely protein, I started to get in trouble with my colleagues. They didn't seem to want to believe that. I mean, who in the world in their right mind would question the protein present in cow's milk? That had almost become legendary as the most awesome and important nutrient of all. I certainly had been raised in that culture.

But as I said, we didn't need statisticians around to tell us what we were seeing. It was there; it was very clear. Honesty is what ought to be driving this research. It's was a matter of being honorable to the research, and it was also a matter of being honest with the taxpayers who pay for our research. I've always felt a great responsibility to the public who pay taxes, some of which goes toward public funding. We got the results, and if it was something that people didn't even like that much (a lot of people didn't), I still felt responsible for telling them what we did with their money. It also meant a lot because there were people getting disease that I thought didn't have to happen. People can be mended. I've come to believe that the whole western model of relying on treating disease at the end stage with harsh drugs is the wrong model. We went down the road many years ago, intentionally or unintentionally, to use drugs to treat the endstage disease, and along the way, we forgot about food. We forgot about nutrition. We never defined it right; we didn't understand it. We've got to get back on track.

JB: When you were talking about your early discoveries, the role of protein in carcinogenesis, the dual effects of exposure to aflatoxin, and higher-protein animal diets, it sounds like it relates closely to the focus of our upcoming 13th International Symposium on Functional Medicine in Tampa next April on biotransformation and detoxification. Having read your papers, it seems that in those animal models, you were looking at certain isoforms of inducible phase 1 cytochrome P450 enzymes that were upregulated by the protein amino acid constitution of higher-animal protein diets. They had a covariable effect on activating carcinogens to biotransformed intermediates, or procarcinogens to carcinogens, which led to an increase of the hepatocarcinogenic load. It's a very interesting gene/environment observation, It's a case study as to how there may be polymorphisms of those genes with different levels of susceptibility, and when higher animal protein diets are added to that, as well as exposure to an imperfect environment, it results in chemical soup. Suddenly, there is a different matrix effect in society as it relates to what medicine is doing, new therapies, and new drugs to treat those conditions. Does that seem like a

reasonable takeaway from your observations?

TC: Yes. I know you have been working in this field for many years, and you said it perfectly. I couldn't say it better.

JB: That leads to a juxtaposition. What you're implying is reduced protein, but with all the insulin resistance, obesity, and diabetes, isn't too much carbohydrate the problem? Cutting down on protein suggests increasing carbohydrate. That seems paradoxical. How do you respond to that?

Low-Carbohydrate Diet
TC: I think the low-carbohydrate diet is one of the greatest hoaxes that has been put on the American public in recent years. It just doesn't make sense, although I have to give credit to part of that story to those who are proposing it. Simple carbohydrates are really what they're talking about, although they use the term, carbohydrates or "carbs." They didn't make it clear that they were talking about simple carbohydrates. They began to question whether high-carbohydrate diets are a problem. The diet I'm talking about that has the greatest chance of reducing and controlling disease is, in fact, a high-carbohydrate diet. They're simply wrong. They didn't really understand, I'm sure, what they were talking about in this regard. When I think of carbohydates, I think of foods that are high in carbohydrates and that means, for the most part, carbohydrates in the natural form, the complex form. That kind of diet is best. The simple carbohydrates like sugar and white flour are not good kinds of carbohydrates. I give them credit for that.

Excess Protein in the Diet
I want to point out one other thing before I forget it. When I'm talking about high-protein diets, I'm obviously not questioning the nutritional value of protein. Obviously, we need protein. It's a terribly important and essential nutrient, and we need it at a certain level. The problem I have with protein, and we explored this in great detail ourselves, is that its effect in increasing cancer, blood pressure levels, and things like that, occurs when we are consuming an excess of what we need. It's the excess protein I am referring to, but unfortunately, and interestingly, most of the American public actually consume excess protein. Some people consume a lot of excess protein, and the low-carb diet people are all of a sudden coming along and talking about reducing carbohydrate intake dramatically. Well, what are they going to replace it with? They're going to replace it with fat and protein. They admit that and they want diets high in fat and protein. While that may lead to what appears to be a short-term benefit, namely weight reduction, for starters, that's not going to last and those people are going to have huge problems in the future by doing it that way.

JB: That leads me to a question related to many studies that have appeared in the literature. I don't want to put words in your mouth, or lead you into an area that is uncomfortable for you, but I have reviewed literally thousands of papers that have appeared in the peer-review literature over the last many decades on the role of macronutrients on physiological effects in either animals and humans. It strikes me that the things that don't get controlled in these diet studies, at least from my observations, are those that are not considered very valuable—the non-nutritive components of plant foods. When they talk about a diet of so many calories percent protein, carbohydrate, and fat in a study, they never control for what the level of all these other, say, non-digestible fibers (that's not always the case because it might be a fiber study), such as flavonoids, polyphenols, or the rich array of phytochemicals that are present in unrefined foods. We look at myriad studies in which one of the more important variables was never controlled for, and then we

make sweeping conclusions about the outcome of the difference between carbohydrate, fat, and protein-rich diets, which really is irrelevant to the way the foods would have affected function if we had controlled all the variables. Am I way off on this?

Healthy Benefits of Plant Food

TC: No. You're absolutely right. There's a whole lot of stuff that is indicated, in plant food, in particular. They contain a whole array of chemicals that have healthful activity. There's no doubt about that. There are the flavonoids, a whole variety of fibrous factions, antioxidants, and so forth. I've been using the word "countless" to indicate the number of different kinds of chemicals that are present in the food we consume, especially in plant-based foods. There's an array of chemicals that, from what we've been learning, have impressive properties. What's really impressive, too, is that those things tend to work together when we consume them in the form of food. There are so many different kinds and, as you said, we don't control for that, for the most part. At least, we ignore them when we're doing our studies. We end up focusing on a few things that we do know something about, but we've ignored all the rest of it that is part of everyday life for all of us when we're consuming food.

JB: At the level of mentorship you are at now, and as a senior scientist with wisdom in this field, do you ever get the feeling that we'll look back at this period of research development period 50 to 100 years from now, and see some of this work as being very silly? We are pursuing new-to-nature molecules for the treatment of disease. We define nutrition in a partitioned fashion, as empty calories, without looking at the full complement. Will we appear as foolish to the future generation as the barber surgeons doing blood-letting in the previous century appear to us?

TC: I've become a little cynical about the way to do science, the way we practice medicine, and especially the way we develop food and health policy. I have been very active in that for a long time, too. I've gotten to the point of referring to our present day as the dark ages of science. Maybe that's too harsh, because we are also learning a lot of great things. Unfortunately, we take the information that we get and try to quickly adopt it to some kind of solution or product or something to sell, without trying to understand it in terms of what nature did for us. That's always what a struggle is about. You do what you think is right from a societal point of view, and you do the best you can. Basically, after discovery, we've done the wrong thing.

JB: If there's any doubt in the minds of our listeners as to how this all fits together, your book, The China Study, is an irrefutable legacy to a different model. I believe that the very exacting work you've done with your colleagues at Oxford and the Chinese Academy of Preventive Medicine collaborative study with Cornell, is a tremendous gift for learning to all of us. Your work, coupled with what Walter Willett and many others are doing to redefine the food pyramid and move out of the box that holds more of the same, as we see the rising epidemic of obesity continue to occur, is where the solutions will be found. I applaud and thank you for your years of dedicated service as a public servant, researcher, and agent of change. Your work is going to make a real difference. I hope everyone who is a thinking person will have a chance to read The China Study.

TC: Thank you. That's very kind of you.

JB: I wish you the very best, and hopefully, we'll catch up with you down the road. Good luck in continuing to fuel the fire of change and spread the news.

TC: I know we're on the same path.

JB: We certainly are, and the best to you.

2005 Nobel Prize for Physiology or Medicine for Bacterium Work

I would like to follow up from Dr. Campbell's comments with one last thought about the concept of a "toxic" diet. In 2005, the Nobel Prize for Physiology or Medicine was awarded to Dr. Barry Marshall, a gastroenterologist from Nedlands in Australia, and Dr. J. Robin Warren, a pathologist at Royal Perth Hospital.[13] They were collaborators in the development of the view that an infectious, opportunistic organism called *Helicobacter pylori* is associated with peptic ulcer disease and some problems related to carcinogenesis of the upper gastrointestinal tract. This was a remarkable discovery. You may recall that they had to fight uphill against medical dogma that held that psychological stress and acid was the cause of stomach and duodenal ulcers. Now, we recognize that it must be a much more complex interrelationship between immunochemical function and stress, and that H. pylori infection is a multiple etiology. Stress may induce altered immune function, which may set the stage for increased prevalence of infection with the opportunistic organism, H. pylori. That ultimately leads to an immune response to the stealth organism embedded in the GI mucosa that induces the normal immunological vigilance, which is associated with the production of oxidants that cause inflammation and tissue damage associated with the ulcer. It is a much more complex etiology than had been previously thought, and the treatment of choice that derives out of this is not just H2 blockers or proton pump inhibitors, but rather anti-infectious medications that euphemistically have been called triple therapy—bismuth, metronidazole, and an antibiotic.

That is an interesting piece of the history of medicine—overcoming bias, seeing the world through a different lens, and commitment to the hypothesis. Dr. Marshall was so committed to his hypothesis that he cultured a whole bunch of H. pylori organisms, orally consumed them, and came down with the infection. In effect, he actually gave himself radiologically-identifiable peptic ulcer disease. That surely is commitment to the hypothesis. It reminds me of the Goldbergers's research, when they injected and ingested the blood and skin scrapings of individuals with pellagra to show that it was not infectious. In Dr. Marshall's case, it was infectious, so that was more problematic. That is such an interesting part of the history of medicine.

It raises the question about opportunistic organisms in the GI tract and their relationship to broad-ranging implications, not just GI disease, but other disorders, as well. That takes us back to a discussion we have had previously in FMU having to do with a toxic diet. What happens if one induces an unfriendly dysbiotic bacterium or parasite to grow in the gut that produces secondary metabolites or some alteration of immune function that could be construed as a toxic response? It is not just the direct effect of the diet; it may also be an indirect effect through the alteration of the GI flora and how that can influence function.

Revisiting the Work of Dr. Andrew Wakefield

We discussed one of the most profound implications of this situation that has neurotoxicity implications, coming from the work of Dr. Andrew J. Wakefield. He has received such incredible notoriety for his observation, and controversy, as well. Dr. Wakefield, a pediatric gastroenterologist at a well-established medical school in London, along with his colleagues, published what is now considered one of the most

classic and a highly controversial papers in the literature. It was so controversial that a board, a censure committee, was assembled to study its veracity, as well as the research and literature that went into it. There were editorials in the *Lancet* that went on for several issues, talking about the study outcome, with responses from Dr. Wakefield. It has been quite a story. The paper was titled "Ileal-lymphoid-nodular hyperplasia, non-specific colitis and pervasive development disorder in children."[14] That was followed up with another paper that appeared in the *American Journal of Gastroenterology*, titled "Enterocolitis in children with developmental disorder."[15]

Dr. Wakefield observed that the ileal-lymphoid-nodular hyperplasia seen in children during a GI exam was uniquely correlated with high prevalence of autistic spectrum disorder (ASD) in children—a kind of cross diagnostic criteria. The more he studied it, the more he thought there was something to it. He attributed some of it to early-stage immunization with measles, mumps, and rubella vaccination (MMR), the relationship it had to altered immune system function through the GI mucosal immune system, and how that could have an effect on brain biochemistry through upregulation of certain components of the immune system, causing brain glial cell immune system dysfunction called autistic spectrum disorder.

This has created a huge controversy, because some individuals in the public health arena thought Dr. Wakefield was attacking immunization, that it would cause prevalence of measles, mumps, and rubella as a result of parental fear, and that there was no strong evidence in the literature that this was true. That was one of those great moments in scientific discovery, not unlike the work of Barry Marshall.

Recently, Dr. Wakefield published another very interesting paper in the *European Journal of Gastroenterology and Hepatology* following up on the same theme, titled "The significance of ileo-colonic lymphoid nodular hyperplasia in children with autistic spectrum disorder."[16] In this paper, he and his colleagues looked at the prevalence of non-specific ileo-colonic lymphoid nodular hyperplasia (LNH) and found that it was significantly geater in the ileum and colon of ASD children, compared with controls (whether or not controls had co-existent colonic inflammation).

Once again, the authors conclude from this more extensive study that ileal colonic LNH is a characteristic pathologic finding in children with ASD and GI symptoms, and is associated with mucosal inflammation. Differences in age at colonoscopy and diet do not account for these changes. The data support the hypothesis that LNH is a significant pathological finding in ASD children. They did, however, find some very interesting features about the diet of children who were on gluten and casein exclusion (grain and dairy product exclusion), who had behavioral improvements that were reported after putting them on exclusion diet. They state:

"The rationale for diet includes the removal of precursors for exorphins with their potential for neurotoxicity. (This would be like casomorphin or glutomorphins.) In addition, the potential for an effect of these diets on the associated intestinal lesion merits consideration, given the immunogenic potential for gluten and casein in the gastrointestinal mucosa."[16]

Many times, children with ASD-like symptoms, when placed on a diet that eliminates gluten and casein, appear to have improved function. That raises the question, are there toxicities in the diet that are unique to the individual, based on each person's immunological vigilance system? Recall that more than 50 percent of the immune system is clustered around the gut. Perhaps it has something to do with the communication between food and the gut mucosal immune system.

This is a fascinating additional chapter to our discussion of what constitutes a "toxic" diet, and how we would "detoxify" a patient who may have immunological responses that have adverse effects on immune system function which, in this case, may weave their way not only through hepatocellular changes and systemic immune system changes, but also central nervous system immune changes, through glial cell activities.

In the editorial that follows Dr. Wakefield's paper, titled "The intestinal lesion of autistic spectrum disorder," Dr. Jeremy Jass reviews the significance of lymphoid nodular hyperplasia in the intestinal tract of children with ASD. He states: "The distinction between physiological and pathological lymphoid hyperplasia of the intestinal tract is of importance in the context of a possible causative link with autism." What we are really talking about is a functional change in the lymphoid system. These are not pathological changes seen in these children. Functional change of this kind of hyperplasia could result in increased intestinal permeability, causing a "leaky gut," to use that term euphemistically.

"This could result in increased intestinal permeability to peptides of dietary origin which may then lead to disruption of neuroregulatory mechanisms required for normal brain development. Alternatively, there could be a primary defect in the translocation and processing of factors derived from the intestinal lumen. These possibilities deserve further investigation and should not be lost in the fog of the controversy regarding the role of measles/mumps/rubella vaccination in the aetiology of autistic spectrum disorder."[17]

My takeaway from all of this, as it has evolved, is that if a child has ASD, clinicians would be well served to at least look at gluten and casein elimination diets to see if symptoms might improve; to look at GI function and health; and to recognize that things like pro- and pre-biotics may be helpful in inducing proper immune function in the gut.

Two Case Reports of the Use of Probiotics in the Treatment of IBD

A recent paper by Drs. Steven Faber, Scott Rigden, and Dr. Dan Lukaczer at the Functional Medicine Research Center, reported improved effects on GI function in individuals with irritable bowel syndrome with theuse of pre- and probiotics." This paper appeared *in Alternative Therapies.*[18]

As we weave all of this together, the term "dietary toxicity" is broader than just that of a poisonous effect. It has an effect on functional physiology through the genomic, proteomic, and metabolomic influence, and a secondary effect through gut flora and its metabolic byproducts that can influence function. I think Dr. Campbell opened our eyes to the important role the diet may play in the myriad chronic, age-related diseases, through the toxic link.

Thanks for being with us. We will see you again in January.p>