March 2004 Issue | Loren Cordain, PhD, Professor Department of Health and Exercise Science

http://jeffreybland.com/knowledgebase/march-2004-issue-loren-cordain-phd-professor-department-of-health-and-exercise-science/

DOWNLOAD AUDIO |

Welcome to *Functional Medicine Update* for March 2004. We are in full swing preparing for this year's symposium, May 11-15, 2004 at the Westin Bayshore Resort in Vancouver, Canada, where we will focus on "The Coming Storm: Reversing the Rising Pandemic of Diabetes & Metabolic Syndrome." This is going to be a remarkable event. I am excited about our slate of plenary speakers and the workshop sessions with "news to use" formats to help with clinical application of the concepts. I believe we will all gain new insight into how to manage this complex and important disorder, the incidence of which seems to be rising to epidemic proportions. I hope you will plan to be with us. I invite you to call the Institute for Functional Medicine at 1-800-228-0622 if you have any questions about the program.

With the symposium in mind, this issue of FMU will focus on aspects of insulin resistance and its relationship to coronary heart disease, diabetes, and inflammatory disorders. These include conditions related to self-proliferative disorders—colon cancer and endocrine-related cancers such as prostate cancer and breast cancer. These conditions may seem at first to be far removed from insulin resistance, but there is a strong, emerging link between insulin resistance and cell-signaling processes related to cellular proliferation of specific tissue types. This link increases the risk and incidence of specific types of cancers and the angiogenic and metastatic processes associated with them.

The Homocysteine Theory of Heart Disease

Before we begin our discussion, I would like to honor one of our long-term FMU subscribers, Dr. Richard Podell, from the Robert Wood Johnson Medical School in Short Hills, New Jersey. For many years, he has written eloquently about themes in preventive medicine. Recently, Dr. Podell published an article that appeared in the journal, *Medical Hypotheses*, titled "Understanding the transition from alternative medicine to mainstream science: the homocysteine theory of heart disease and the crucial role of effective mentoring."[1] I want to compliment Dr. Podell on this article. He used as an example of how science resists change, Kilmer McCully's hypothesis that hyperhomocysteinemia is associated with increased risk to vascular disease, and not just a digital, but rather a graded increasing risk, depending upon homocysteine plasma concentrations. It is not whether you have it or not; you may be at higher risk with increasing homocysteine plasma levels.

That hypothesis faced a lot of resistance by "mainstream medicine" for more than 30 years, but Dr. McCully was committed and quite diligent about pursuing his theory. Even in the face of criticism and

adversity, he was able to eventually mount enough persuasive information to get his colleagues to look at the concept more in depth, resulting in a paradigm shift over the last few years.

Dr. Podell uses McCully's homocysteine theory of heart disease to describe the transition from what may have been considered alternative at one point to incorporation into the body politic of mainstream medicine. It is always ironic, because when that transition occurs, it seems that it was initiated in the mainstream and never existed prior to that, even though the theory may have a 30-50 year precedent before it is finally accepted.

Dr. Podell uses an interesting format in his article. He asks some questions and then answers them. For instance, why is alternative medicine science so weak? What practical steps might we take to foster a more rigorous research approach? He uses the McCully hypothesis as an example. When McCully first proposed the homocysteine theory of heart disease (HTHD) in 1969, mainstream medical science vigorously rejected both the theory and its author, especially in the US, because it was thought that heart disease was primarily the result of high cholesterol. The cholesterol hypothesis was dominant; it was not politically favorable or fashionable to be speaking against that concept. If research money is sought to investigate something that people do not consider potentially important, the money is usually not forthcoming and science cannot be amassed in support of new concepts. It almost becomes a self-fulfilling circular reinforcement of a preexisting dogma, and it is difficult to break away and support an alternative hypothesis. The problem is that people say there is no research to support the new hypothesis and the cycle continues, like a dog chasing its tail.

Dr. Podell asks: "Why was the HTHD first rejected so fervently? What factors, two decades later, resulted in its revival?" He suggests there was a changing philosophy and a changing paradigm slowly emerging as a result of the concept Linus Pauling described in his 1949 landmark article on sickle cell anemia, in which he used the term "molecular medicine." Dr. Pauling proposed that many disorders that later evolve into various diseases are locked into genetic soil and play out through the interaction of genes and environment to give rise to the diseases. Heart disease is not an infectious disease or a traumatic disease; it is a metabolic disease. This emergence stemmed from the work of Sir Archibald Garrod's concepts of metabolic genetic inborn errors of metabolism. Pauling then talked about the role that various natural molecules, which he termed "orthomoleculars," have on the modification of the internal milieu of the body and the promotion of physiological function. From that came the discovery that specific nutrients, which are natural substances in the body, could be used at higher levels to promote specific enzyme function and push sloppy equilibrium and physiological chemistry toward completion. This results in optimization of function in individuals who may have had what we now call genetic polymorphisms that lead to sluggish reactions. Rather than changing genes, promotion or improvement of optimal function is achieved by pushing for equilibrium through a mass action effect with administration of higher levels of a cofactor—the vitamin, mineral, or nutrient factor.

This was an interesting new concept in medicine, well described in a landmark article published in *Science* magazine in 1967 by Dr. Pauling, titled "Orthomolecular Psychiatry." The article was not well received or understood by those in the traditional medical world because it spoke in physical chemistry terms about enzyme binding, reaction rates, and kinetics. These things were probably not on the minds of most practicing physicians at that time. It did provide a formalism by which one could understand some of the things Dr. McCully was speaking to. A broader body of understanding began to build based upon some fundamental principles: in this case, the Pauling principle of orthomolecular medicine; and later,

mega nutrient therapy.

Increasing interest began to grow on the part of other investigators to conduct research on homocysteine. Classic papers were published from 1980 through 1985, such as those written by Malinow, Kang, Taylor, et al., which demonstrated that McCully's hypothesis warranted further research. From the 1980s until the year 2000, there was finally some public acceptance of McCully's homocysteine hypothesis. This resulted in some public health policy decisions about homocysteine and the B vitamins. There was finally some agreement that the B vitamins could modify function through activating sluggish enzymes involved in the metabolism of homocysteine. That led to a transition of increasing interest in the 1990s. The number of papers and citations in this area increased dramatically as the new concept became more favorable and fashionable. It was finally considered an "OK research project" for an academic or medical researcher to be involved in. It became a new "head of steam" producing its own paradigm shift. The timeline I am talking about—1969 to 2002—is a period in excess of 32 years. That is a pretty remarkable latency period during which people still saw the theory as "alternative" until it finally "clicked over" and became part of the mainstream.

Dr. Podell proposes that we need a conference to discuss controversial areas and share broad disciplinary input, and suggests the topic of diabetes, which we will focus on at our 11thInternational Symposium on Functional Medicine. He proposes that the National Institutes of Health, the American Diabetes Association, and other prominent institutions convene a weekend conference of perhaps 20 leading diabetes scientists, including those doing controversial work that is not in the "mainstream." This would help foster and stimulate new ideas and new research concepts that might lead to faster development of potentially successful therapies. It might also break down barriers and start building bridges across different disciplines. This is a laudatory call for action and certainly has potential for positive outcome if we could suspend our disbelief, work together across disciplines, and look across perceptions about how to solve these problems.

I want to thank Dr. Podell. He has helped us to understand some of the barriers we have talked about so many times over the last 20 years in FMU as to why certain of these concepts take so long to finally become absorbed into practice.

ny questions about the program.

With the symposium in mind, this issue of FMU will focus on aspects of insulin resistance and its relationship to coronary heart disease, diabetes, and inflammatory disorders. These include conditions related to self-proliferative disorders—colon cancer and endocrine-related cancers such as prostate cancer and breast cancer. These conditions may seem at first to be far removed from insulin resistance, but there is a strong, emerging link between insulin resistance and cell-signaling processes related to cellular proliferation of specific tissue types. This link increases the risk and incidence of specific types of cancers and the angiogenic and metastatic processes associated with them.

The concept of modifying insulin sensitivity and improving glucose transport is another area that falls under the potential rubric of alternative therapies. There are those who have been arguing for dietary and lifestyle interventions that are not considered within the scope of the American Diabetes Association, but they are starting to accept alternative interventions as possibly being effective and having validity.

I am reminded of Robert Atkins' interesting hypothesis. I met Dr. Atkins in the early 1970s. His concept of weight loss using ketogenic diets (high in protein and fat and low in carbohydrate) was observed to be useful from an empirical standpoint. There was no question that patients who went on the Atkins Diet lost weight rapidly. It was argued against because the loss of weight was principally due to the diuretic effect of the diet (loss of water), and it was felt that you could not lose 10 pounds of fat in a week. Some patients said they lost 10 pounds in a week, but thermodynamically, it was felt that it would not be possible to lose that much weight in a week's time unless one was training for an athletic endurance performance. People were told they were losing water and electrolytes and increasing ketone and triglyceride levels, which is not good. They were cautioned they might experience metabolic acidosis. Some people who were poorly controlled on this program did have problems. The diet was looked upon as one outside of the mainstream. Yet, it may have had some unique metabolic effects on insulin, cell signaling, adipocyte physiology, and the interrelationship between fat mass and central system function that controls messages related to appetite control and thermogenic response. It was not accepted that a dietary approach with higher protein/higher fat and lower carbohydrate was reasonable.

Thirty years later (again, this timeline seems to be interestingly coincident), there were things about the higher protein/lower carbohydrate diet in certain individuals (now called carbohydrate sensitive or dysglycemic), that may account for the remarkable improvement in their body composition. Lowering simple carbohydrate, insulin-mediated responses, and glucose transport difficulties improves cell signaling and has a positive impact on glucose transport and gene expression—things like protein tyrosine kinases that regulate various aspects of cellular function, and lower cellular proliferation and inflammation. These are interesting outcomes from such a simple thing as changing the ratio of carbohydrate to protein to fat.

Over the last 30 years, the story has changed as we have learned more. Now, we recognize that the Atkins Diet is not just eating all the fat and protein you want and not eating any carbohydrate. Again, it is eating the *right* protein and fat, and it is not necessary to rigorously exclude all carbohydrate, but certainly that which has a high glycemic load contribution, leading to increased insulin and impairment of glucose transport. This approach has been refined, but certainly the perception that increasing protein and lowering carbohydrate, particularly the refined simple carbohydrates that have become so predominant in our processed diet, does have a beneficial and salutory effect on insulin dynamics. Insulin activity is much more than controlling blood sugar; that is the interesting part of the story. Insulin activity also has an influence on the regulation of the expression of certain genes, changing the cellular architecture of the way the cells are expressed, which is more than glucose transport alone. Many functions can be altered, such as the expression of inflammatory mediators and various types of peroxisome proliferation and activity that relate to fatty acid metabolism.

As a consequence of 30 more years of research, we are now recognizing that there are some extraordinary physiological influences of an altered protein/carbohydrate/fat diet on fundamental processes that affect the human genome and are expressed into the phenotype.

This is the "new look" of dietary protein in diabetes. An editorial which appeared recently in the *American Journal of Clinical Nutrition,* addressed that topic.[2] Dr. Robert Eckel talks about new clinical research being published showing that an increase in dietary protein improves blood sugar response in people with type 2 diabetes. Mechanistically, it occurs through alteration of the cellular signaling process pertaining to insulin mediation and how that interrelates with a variety of other gene

response expression patterns having to do with insulin sensitivity and insulin levels. We need to change our view of how protein, fat, and carbohydrate may serve as macronutrients in the modification of gene expression and the regulation of function. Dr. Eckel says that we have to be cautious not to overdo any specific model and assume it is the answer to all problems related to insulin resistance or to diabetes.

“Many myths about protein and diabetes control need to be recognized. Although nonessential amino acids may promote glucose production, plasma glucose does not increase after protein ingestion. Moreover, increases in dietary protein do not promote sustained elevations in glucose, slow the absorption of dietary carbohydrate, or accelerate the increase in plasma glucose in response to insulin-induced hypoglycemia.”
Dr. Eckel also points out that any diet model can be taken to the extreme. Someone who reads this might wind up thinking protein is great and carbohydrate is bad, and decide to get the majority of calories from protein. That would be considered an extremist position. Why do I say that?

Let us assume, for the sake of argument, that a person is on a 2400 calorie-per-day diet, and will get the majority of calories from protein—let’s say 50 percent. Fifty percent of 2400 calories is 1200 calories and there are 4 calories per gram. How many grams of protein would be consumed on a daily basis? It would be 300 grams. Is the average liver and kidneys of an individual capable of processing 300 grams of dietary protein a day, and maintain good functional health over time? The answer for most individuals would be no. That would be considered a very high load of nitrogenous molecules that the body has to deal with through the urea cycle and then through the urogenital system, in order to properly manage and metabolize that level of dietary protein.

Clearly, overwhelming the body’s machinery for handling amino acid protein metabolism could take the model of good protein/bad carbohydrate to an extreme. Also, this does not speak to the type of carbohydrate. There is a significant difference in the glycemic load effect of a simple carbohydrate with rapid kinetics of absorption and dramatic effects upon metabolic function, versus a slow-release complex carbohydrate wrapped up in unrefined plant fibers, both soluble and insoluble, with different kinetics and different effects on glucose dynamics. Using the terms “protein” or “carbohydrate” could be misleading. We need to be specific about the type of protein and carbohydrate, and differentiate from things like simple sugars, partially hydrogenated vegetable oils, or saturated fats. Even things in the protein family that might be considered heat-damaged proteins with heterocyclic amines could be toxic and have carcinogenic potential. Sometimes we lose the real specificity by using general terms

A paper in the *American Journal of Clinical Nutrition* discusses an increase in dietary protein resulting in improved blood glucose response in people with type 2 diabetes.[3] This is certainly encouraging. This paper describes a study in which the ratio of protein to carbohydrate to fat was varied in two diets. The ratio of protein to carbohydrate to fat was 30:40:30 in the high-protein diet and 15:55:30 in the control diet. In this washout, crossover study, it was found that the high-protein diet lowered blood glucose postprandially in persons with type 2 diabetes and improved overall glucose control. Glycated hemoglobin decreased 0.8 percent and 0.3 percent after five weeks of the high-protein and control, diets, respectively. Triacylglycerol was significantly lower after the high-protein diet than after the control diet. Insulin, C-peptide, and free fatty acid concentrations were not significantly different after the two diets. The investigators suggest that longer-term studies are necessary to determine the total magnitude of response, potential adverse effects, and the long-term acceptability of the diet. It is encouraging that dietary protein appears to exert a beneficial effect in modifying the glycemic response to diet

There has been a longstanding controversy about whether sugars do or do not have adverse effects on glycemic control. It is my strong belief from what has been published over the last few years that in individuals with impaired insulin sensitivity, the higher-sugar diet has a deleterious effect on normalizing blood sugar. It is not total carbohydrate alone, but also the simple carbohydrate that needs to be modified. This topic is discussed in another recent paper in the *American Journal of Clinical Nutrition*, titled "Sugars, insulin sensitivity, and the postprandial state."[4] Mark Daly discusses that the pattern of postprandial responses elicited by sucrose and fructose differs substantially from that elicited by starches, and that they may offer a potential explanation for the conflicting results on insulin sensitivity. It is possible that increases in insulin exposure may affect insulin sensitivity through downregulation of insulin action.

The concept of normalizing insulin response to the diet might apply to some of our thoughts about vegetarianism. The vegetarian diet has historically been modest in protein, much higher in carbohydrate, and modest in fat, but the fat has generally been that of highly unsaturated vegetable oils, polyunsaturated fats. If protein is really the determinant for lowering insulin response, then why is it that people on an unrefined, complex carbohydrate vegetarian diet appear to experience beneficial effects on the regulation of insulin and glucose?

That is why I have been emphasizing that it is not protein alone; it is the full complex of the matrix of the diet. This comes from some work recently published in the *American Journal of Clinical Nutrition* by David Jenkins on type 2 diabetes and the vegetarian diet.[5] Dr. Jenkins will be a presenter at our 11th International Symposium on Functional Medicine in May, and is one of the world's most well known investigators on the relationship between insulin sensitivity and carbohydrate nutrition. He is one of the fathers of the concept of the Glycemic Index. He says the vegetarian diet contains a portfolio of natural products that help to regulate insulin sensitivity. It is not just the complex carbohydrate and the fiber; it is also the phytonutrients in a rich, unprocessed, natural, high complex carbohydrate diet that help to regulate insulin sensitivity and cell signaling. White flour and sugar are quite different from colored fruits and vegetables in their natural composition and the way they can contribute to regulating insulin. Protein is important, but the type of carbohydrate and its role in a complex vegetarian diet is important, as well. The takeaway is that both Atkins and Pritikin were right.

What Nathan Pritikin and, before him, Dr. Lester Morrison at UCLA talked about, was not wrong. A high complex carbohydrate, unrefined, high fiber diet will help to normalize blood sugar and lower the risk to diabetes and cardiovascular disease. It is not that our physiology has suddenly changed and requires a high protein diet. It is the nature and the form of these ingredients in the context of the highly processed white-type diet that we are consuming today—the diet of convenience—that may feed into dysglycemia and the pandemic of type 2 diabetes.

This is also the model that Dr. Dean Ornish has spoken to very effectively from his studies and the discussions we have had with him in FMU (December 1990, May 1992). We need to be cautious not to throw the baby out with the bath water and claim that protein is good, carbohydrate is bad, and the best approach is to eliminate carbohydrate from the diet. There is no evidence to support that. It is the type of dietary protein, carbohydrate, and fat that seems to play the important role.

If we examine the contribution of vegetarian diets to health and ask if we are seeing a paradigm shift, I believe it is the type of vegetarian diet. Is it adequate in protein? Is it a diet using unrefined fruits,

vegetables, grains, and legumes? Or, is it vegetarian meaning potato chips, Coke, and French fries? That is a high carbohydrate diet, too, but one that contains the wrong kind of carbohydrate.

That is what Dr. Joan Sabatè talks about in a recent editorial in the *American Journal of Clinical Nutrition* on the changing paradigm.[6] She discusses a vegetarian diet that will improve insulin sensitivity and vascular function, reducing the risk to both diabetes and heart disease.

You will be hearing much more about this from the experts in the field who will be presenting at our May symposium. It is inappropriate to focus on percentage calories of macronutrients and assume that we now have the perfect diet—the concepts of 40/30/30 or 15/30/45, or whatever the ratios might be. We tend to think that the numbers are the control factors, when it is really what makes up those numbers. What is the type of protein? What is the type of carbohydrate? What is the type of fat? Significant variations in glycemic response and insulin dynamics can occur based upon the composition of each of those macronutrients, as much as the ratio percentage. That does not mean that increasing dietary protein is without benefit in individuals with impaired glucose tolerance or insulin resistance; it is to try to put this argument or perspective into context.

It also relates to the presence of various micronutrients in the diet, not just macronutrients. What is the nutrient density of the B vitamins that we know are extraordinarily important for carbohydrate metabolism? We have heard from Dr. Derrick Lonsdale, an eloquent clinician/presenter on FMU many years ago (September 1992, April 1998), who talked about transketolase as an important enzyme for carbohydrate metabolism and the role of vitamin B1 (thiamin). Many people may have a functional thiamin insufficiency that requires much higher levels of thiamin to drive their transketolase and improve their carbohydrate metabolism. They could have a functional vitamin insufficiency that is not recognized that produces carbohydrate craving and a “sweet tooth.” Thiamin does not work by itself; it works as part of the B complex family in balance with riboflavin, pyridoxine, cobalamin, and folic acid. All of these vitamin B family complex members work together to help regulate energy metabolism.

What about trace minerals? Chromium also plays an important role in insulin signaling through glucose tolerance factor. This topic is nicely reviewed in a recent paper by Drs. Anne Dattilo and Stanley Miguel, titled “Chromium in Health and Disease,” that appeared in *Nutrition Today*.[7] They review the work of Dr. James Anderson on the role of increasing dietary chromium in improving insulin sensitivity and glucose transport. Doses or intakes of chromium in the hundreds of micrograms-per-day levels may be beneficial for individuals who have a certain type of insulin resistance or impaired glucose response.

Like all nutrients, a little is good; a little more may be better, but a whole lot more may not be better. We should not jump to the conclusion that if an individual does not get a response at a certain level, that the dosage should be increased. Everything has a parabolic dose response curve—coming up the side of the curve to optimal function with increasing concentration, and going down the other side of the curve to reduce function with toxic intake of a substance. With chromium, there is also potential for adverse effects. According to the clinical work on this trace mineral, over 1000 µg per day may be inappropriate unless following a specific uniqueness in a patient in which potentially adverse effects might result. According to the review, a range of 100 to 1000 µg per day is probably in the safe range. Chromium may play an important role in helping to stabilize insulin response.

There are also a number of studies showing that vitamins C and E improve insulin sensitivity. The

polyunsaturated fatty acids of the omega 3 family also appear to have a beneficial effect on insulin sensitivity. Shifting away from a partially hydrogenated vegetable oil diet to a more fish oil-based or plant unsaturated oil-based diet rich in omega 3s, such as flaxseed oil, may be beneficial in improving insulin sensitivity.

The point I am trying to make is that there are many variables and nutritive factors that play a role in helping to send the right message from insulin to the cell to improve and normalize glucose transport. I have not gone into phytochemicals in plants, like flavonoids, glucosinolates, and polyphenolic compounds that can influence insulin sensitivity. We are going to learn much more about those and why they may be important contributors in a complex unrefined diet for improving insulin sensitivity. It is not just the macronutrients or the traditional vitamins and minerals. There are other substances found in plant foods that may help to regulate insulin sensitivity.

We have had difficulty in making the transition to the food of commerce, the food of convenience, the food of white sugar, white fat, and white flour, with nominal nutrient fortification to prevent scurvy, beri beri, pellagra, xeropthalmia, and rickets. That diet appears to be associated with increasing prevalence of metabolic syndrome. That diet, coupled with lowered exercise patterns and perhaps other factors such as stress, as discussed in a recent cardiology review, starts the clock ticking. The ticking clock is heading toward increasing atherosclerotic and diabetes risk. This is discussed in an interesting review that appeared in the November 2002 issue of *Cardiology Review*,[8] talking about what happens physiologically as insulin resistance increases. Microvascular outcomes occur as a consequence of metabolic syndrome, and this increases cardiovascular risk, as well as peripheral vascular injury, neurologic injury, peripheral neuropathies, and ocular injury. Nephropathic problems occur downstream with a loss of kidney function. These are big problems that occur over periods of time. Well before the person may be diagnosed as having diabetes, they may be experiencing these adverse effects.

Optimizing insulin sensitivity plays an important role in the prevention of “age-related dysglycemic events.” The thiazolidinedione family of drugs has been used to improve insulin sensitivity through activation of the peroxisome-proliferated activated receptors (PPARs), but there are natural substances in the diet that are PPARγ agonists. If diets are consumed consistent with physiological needs, some of the messages for PPAR agonists are sent free of charge. Medications may not be necessary.

As the mechanism of insulin resistance is explored, including some of the effects from certain drugs such as metformin, the sulphonylureas, or the thiazolidinediones, it is recognized that dietary factors play roles in the mechanisms the drugs are attempting to treat. They share common pathways. When we eat food that contains the right nutrients, it results in the right physiologic effects. Foods we frequently consume may send altered signals to dysfunctional pathways, for which we sometimes use various medications to modify, block, or alter.

As insulin goes up and insulin resistance increases, other secondary endocrine disturbances occur in the metabolism of DHEA through cortisol and into androgens and estrogens. We now know that the steroid dehydrogenase enzymes can be modified in their function by high insulin levels, particularly in theca cells in the ovaries of women. Increasing incidence of polycystic ovary syndrome (PCOS) through hyperandrogenicity is associated with insulin resistance, as well as menstrual dysregulation, menorrhagias, and changing body architecture such as the apple-body shape in women that may occur as a result of a shift in androgen. The insulin resistance/hyperinsulinemia syndrome has a multiple series of

effects on endocrine function, thyroid function, sex steroid hormone function, and cortisol function. It is not just blood sugar alone. That is the model that is starting to emerge.

There is a good paper in *Medical Hypotheses* discussing the relationship between postprandial insulin and visceral vs. gynoid adiposity.[9] The apple-body shape (increased waist-to-hip ratio) seen in some women, which may include growth of facial hair and what appears to be male-like shifts in physiognomy, is associated with insulin resistance/hyperinsulinemia and altered postprandial insulin sensitivity. Managing the mechanisms of insulin signaling involves more than just the risk to diabetes. There are microvascular, macrovascular, and endocrinological impacts that cut across many different conditions, diseases, and subspecialties of medicine. Diet and lifestyle play principal roles in establishing the tone of how genes are expressed into these signaling pathways. For instance, they may help to normalize function or create dysfunction that is finally diagnosed as PCOS. PCOS is the last stage of a series of events that promote increasing androgenicityin women, with dysfunctional impact on ovarian function with lowered estrogen and increased androgen concentrations. It is not whether or not you have PCOS. There is a graded effect of increasing relative risk with increasing insulin resistance.

This is another important part of the functional medicine model which shows graded effects from complete absence of function, which we call pathology and perhaps death, to the presence of optimal function, and every stage in between. It is a graded series of stages. Diagnosis is often dependent upon crossing a specific threshold that we call the disease threshold. On a functional basis, there is a whole range of different functional states that may precede the onset of disease or diagnosis associated with disability, lowered quality of life, or chronic illness. That is the stage where functional medicine, based on physiological mechanisms, can play its most important role.

I hope I have given you some insight into insulin resistance and dietary relationships, and the protein/carbohydrate/ fat connection. We will move to side 2 to continue this discussion.

INTERVIEW TRANSCRIPT

Clinician of the Month
Loren Cordain, PhD, Professor
Department of Health and Exercise Science
Colorado State University
Fort Collins, CO 80523

JB: It’s time for our Clinician/Researcher of the Month. Over the years in FMU, we have been fortunate to listen to some voices of great clarity on complex issues pertaining to lifestyle, health, environmental issues, and chronic disease. This month is no exception. We are privileged to have Dr. Loren Cordain as our guest. Many of you may be familiar with his work. He is the author of the book, The Paleo Diet, which was brought to my attention by one of our physician subscribers. He suggested I read it because it would “fill in a lot of gaps.” That turned out to be a good suggestion. The book is well written from very interesting anthropological and physiological perspectives.

Dr. Cordain received his PhD in Health from the University of Utah in 1981. He has been employed as a professor in the Department of Health and Exercise Science at Colorado State University for the past 21 years. His work has been highly publicized.

Having looked over your C.V. and observing how many years you have been engaged in exercise science and the relationship of exercise to physiology, my first question is how did The Paleo Diet concept emerge?

Emergence of The Paleo Diet Concept

LC: Thank you, Jeff, for the kind words regarding my book and our research. By the way, we have a website, www.thepaleodiet.com, and your readers can download all of our scientific papers. We have roughly 30 to 50 papers and abstracts available on this topic. The book itself was written based on our scientific findings in hunter-gatherer societies.

About 15 to 20 years ago, I read Boyd Eaton's seminal paper in The New England Journal of Medicine, titled "Paleolithic Nutrition."[10] I thought it was just about the best idea I'd ever heard of. I read all the cross references in that article, which generated even more cross references that opened up a gigantic spider web of articles. I began to form files on all the topics and started making connections. In the early 1990s, I finally got up enough courage to call Dr. Eaton at Emory University and had him come to Colorado State University, where he gave a talk. We hit it off and started publishing papers together. Paleolithic nutrition is a passion of mine and whether I get paid to do this work or not, I'd be doing it. It is simply my passion.

JB: That rings true very strongly in your work in which there is obviously a strong mission-driven component. For those listeners who might be unfamiliar with the concept of the Paleo Diet, perhaps you could give us a brief overview before I ask you how it interrelates with some other current diet controversies.

Overview of The Paleo Diet

LC: I think you've really hit the nail on the head, Jeff. There are probably as many opinions about what the optimal diet is as there are people on the planet. Initially, when I set out, my original goal was to find the optimal healthful diet for myself. One way of doing that would be to look at every single possible diet to try and find out what would be the best one. But I thought there must be a more powerful and leveraging procedure to do this, and indeed there is. Dr. Eaton's concept is that our nutritional needs are determined by our genes. I don't think anybody in your audience would argue that; the fact that we require omega 3 fatty acids or vitamin A is because our cells need them. Why do our cells need them? They need them because our genes are building proteins.

The next question that arises is what shapes our genes? Why is an animal a herbivore, another animal a carnivore, and another animal an omnivore? Why have they adapted to different diets? The reason for that is natural selection. It's the environment the animal evolved in. That is really a biological action that goes without saying, that animals are optimally adapted to their environment and the foods that are found there. Humans are no different than any other animal. What Dr. Eaton proposed was that if we go back to the time when all humans were in their native ecologic niche, the hunter-gatherer niche which was, evolutionarily speaking, very recent. Only 500 generations ago, every human on the planet was a hunter-gatherer and the only foods we could eat were those that were minimally processed wild plant and animal foods. We've gone back into the fossil record. We've also examined the diets of modern-day hunter-gatherers to determine what they have eaten and what they haven't eaten. The most enlightening part of all of this is what they don't eat. What we're finding now from clinical studies is that increasingly, the foods they don't eat are those associated with health problems and illnesses.

JB: That's a very interesting model. The concept is that it's not just the bad stuff we put in food, but also the good stuff we take out. When you look at how these dietary changes over the last 50 or 60 years have impacted health, where do you find the biggest differences between the Paleo Diet and today's diets of convenience?

Differences Between Today's Diet of Convenience and The Paleo Diet

LC: It's very astute of you to realize that it's not just what we took out; it's also what we put in. This process began 10,000 years ago with the domestication of cereal grains. Increasingly, as we ate more cereal grains, something had to give. Something had to be reduced in our diet. We started eating less animal products and less fruits and vegetables. Animals were domesticated at about the same time—10,000 years ago—so we started to include dairy products in our diet. As we include dairy products and cereal grains in our diet, we displace fruits and vegetables, wild lean meats, and seafood. That process accelerated as more and more Neolithic foods came into our diet. For instance, salt was first observed being mined in Europe roughly 6,000 years ago. Prior to that time, very few people had any sort of processed salt in their diet. Except for honey, we ate no processed sugars. Refining sugar didn't happen until about 1,000 years ago in India, when it was observed for the first time. Since the Industrial Revolution over the course of the last 200 years, we have increased our sugar intake.

The same thing can be said about cereal grains. Cereal grains, up until about 200 years ago, were all consumed in their whole form. The procedures to mill cereal grains that produced very fine flour, removed the germ and the bran, were only introduced in steel roller mills in the 1880s. The same thing can be said about high saturated fat meats. Prior to about 1850, all meats that were consumed in this country were basically grass-fed. With the advent of the steam engine, the reaper, and other mechanized industrial tools, we were able to bring cows and corn together and produce feedlot-fed animals. Today, 99.9 percent of the beef, chicken, and pork we consume has been produced in a feedlot. This is very fatty meat compared to that of an animal produced in the wild. Dramatic changes have occurred. Trans fatty acids only came about by the hydrogenation process that was invented in 1897. All of these changes have occurred in our diet, including those resulting from refrigeration. We have come a long way, but way beyond foods that we were genetically adapted to eat.

JB: One of the points I have been trying to make in our discussions over the last several months is that these foods you've been describing are more than just nutrients; they are also signaling molecules. They impart signals picked up by response systems that alter gene expression patterns. That shapes both our physiology and our physiognomy. That's why people start looking different. We start seeing more apple-body shaped people with morbid obesity. The reflection at the phenotypic level of what is occurring at the gene response level is a manifestation of how these food changes interface with our gene potential. Is that consistent with the model you're describing?

Research on Diet and Acne

LC: That's absolutely correct. I'm not familiar with the level of sophistication of your audience, but we can go into that kind of detail. For instance, we published a paper in the Archives of Dermatology, probably the finest scientific medical journal on dermatology.[11] The official position of the dermatology community had been that diet and acne were completely unrelated. We traveled to a population of hunter-gatherers, the Ache people in Paraguay in South America, and followed them over a two-year period. It was a small group of about 118 hunter-gatherers. Some of the anthropologists in our group followed them over a two-year period and we had physicians in the field with the anthropologists.

We didn't find one case of acne in any of the adolescents or any of the adults.

We went further to a remote island off the coast of Papua New Guinea called Kitava where there are about 3000 people. A member of our research team, Dr. Stefan Lindeberg, examined these folks cross-sectionally over about a four-month period. We examined more than 300 adolescents and didn't find a single case of acne. If you were to look at a population of 300 adolescents in the United States, roughly 80 to 85 percent of them would have acne. That led us to the idea that there had to be something going on environmentally that was responsible for the vast differences between the acne incidence rate in non-Westernized versus Westernized people. We found that even though the diets between the Ache in Paraguay and the Kitavans on the remote island off the coast of Papua New Guinea were vastly different, they did have similar characteristics, in that the carbohydrates they ate were all low-glycemic-load. Our research group believes, and we set up a mechanism for this, that high-glycemic-load carbohydrates such as refined flours, sugars, potatoes, chips, and processed foods found everywhere in the Western diet, set up a situation where insulin is chronically elevated. When insulin is chronically elevated, other hormones are elevated, as well, and other hormones are reduced. There's a hormone called IGF-binding protein-3 that is reduced. It turns out that IGF-binding protein-3 is a ligand for an endogenous retinoic acid receptor. Retinoic acid is involved in the proliferation of cells at the gene transcription level. We believe that acne represents unregulated tissue growth, first at the endothelial cells that surround the hair follicle. Acne is a plugging of the hair follicle by excessive endothelial cell growth and it results from excessive sebum production. When insulin is chronically elevated, it also tends to elevate androgens, or the male hormone. The male hormone is responsible for producing more sebum. It actually works at the gene transcription level. Food and genes are intimately related, and they are phenotypically expressed as health and disease. That's just one small example of how our group has been challenging the status quo and has been on the leading edge with our research.

JB: I had a chance to read one of the papers in the Archives of Dermatology on the research you just discussed. I thought it was very well done, and both provocative and substantial in its support.

LC: Thank you. I just want to mention to your listeners that we also have empirical intervention data that supports that research. What we had originally done resulted in epidemiologic data. Now, we have dietary interventions. We completed a trial in Australia in which we took 75 adolescents who had acne and put them on a high-protein, low-carbohydrate type diet, similar to what the Paleo Diet is all about. We had a dramatic reduction is acne incidence rates in the group, and complete elimination of acne in many of the subjects.

JB: That obviously segues nicely into a companion question. Another of your papers which is equally interesting is titled "Hyperinsulinemic Diseases of Civilization—More Than Just Syndrome X."[12] One of those diseases we've been talking about is acne. Would you tell us a little bit more as to how you see hyperinsulinemia fanning out into other disorders of aged populations?

Disease and Elevated Insulin Levels

LC: With syndrome X, I think many people think about type 2 diabetes, obesity, hypertension, and dyslipidemia—the characteristic diseases. We determined that diseases of unregulated tissue growth are related to a chronically elevated insulin level. Insulin is a very potent anabolic hormone, meaning that it stimulates growth in all tissues. It does that via a number of hormonal cascades that I described. It tends to elevate androgenic hormones and it tends to influence the IGF-1/IGF-binding protein 3 growth

hormone axis, all of which tend to promote growth. Growth is very good during adolescence, and also during the later years, but it also needs to be regulated. We find that perturbation of these hormones after the growth period tends to promote epithelial cell cancers. Epithelial cell cancers are those such as breast, prostate, and colon cancers. We believe that high glycemic load carbohydrates are environmental dietary factors that underlie these diseases. Epithelial cells are those that have very rapid turnover, so the cells in the colon, in the milk ducts in the breast, and in the prostate, have very rapid turnover. Therefore, they are highly responsive to 24-hour changes in hormones. High glycemic-load carbohydrates manifest themselves as epithelial cell cancers because they are so susceptible to changes in IGF-binding protein 3, IGF-1, and insulin.

JB: That leads to a common question. Is carbohydrate bad and protein good? Should we shift our diet almost predominantly to protein and leave carbohydrate behind because it's a bad substance in the diet? From what you've said and also indicate in your book, we need to put the type of carbohydrate, protein, and fat in perspective. Perhaps you would comment on that.

Ratio of Carbohydrate and Protein in the Diet

LC: That's right. It's primarily a qualitative rather than a quantitative issue. We believe that by elevating protein in the diet, it can have beneficial effects. In light of the Atkins Diet, some clinicians believe you can consume an unlimited amount of protein in the diet, but that's not true. We pointed that out in a paper we published in the American Journal of Clinical Nutrition in 2000.[13] All people have a physiologic protein ceiling and that ceiling is based on how much urea is excreted. One of the byproducts of protein metabolism is urea, which is toxic. The body needs to get rid of urea. It does so in the liver and there are enzymes that allow urea to be turned into other products. But those enzymes can't be infinitely upregulated. It turns out that roughly the maximum amount of protein you can eat in your diet is between 30 and 40 percent of your total energy if you're in a equicaloric situation, meaning normal calories. There is a limit to protein consumption, and above and beyond that, protein becomes toxic. We believe there is a fine line. The amount of protein one gets in the typical Western diet is about 15 percent of our energy, and we're eating roughly 50 percent carbohydrate. Increasing protein by 10 to 15 percent, up to 25 to 30 percent of your energy, with a subsequent reduction in carbohydrate and an increase in good carbohydrate (low glycemic-load carbohydrate), will have beneficial effects on the hormonal cascade that I've been speaking of.

JB: In your book, you describe how one can go about achieving that objective you just described without falling back to the premise that protein comes in high saturated fat forms. Perhaps you can describe how this all gets woven together in a complex agricultural-based society with agri-businesses being the watchword.

Diet in a Complex Agricultural-Based Society

LC: You have brilliant insight into what's going on. In the 1950s, we basically threw out the baby with the bath water. We decided that red meat was bad. We should have thrown out two things—the saturated fat that came with the red meat, and the way red meat is produced. We are feeding our cows corn, which is very high in omega 6 fatty acids. We also feed them sorghum. The cereal grains are very high in omega 6 and they produce an obese animal with high saturated fat. The membranes within the meat itself are very low in the healthful omega 3 fatty acids. Inadvertently, we produced big, fat animals resulting in juicy, red steaks that everybody liked, but we produced a very unhealthy product. In the 1950s, when we realized that the LDL receptor was downregulated by certain saturated fats, it became apparent that red meat was a bad thing, but we didn't look beyond that. As I said, it's a qualitative rather than a

quantitative issue. If we could get healthy, lean meat as we do healthy seafood (providing it doesn't have heavy metals in it), it's a very healthful substance, one that we've evolved on and one that makes our physiology very correct.

It's a similar situation with grains. Whole grains are clearly much better than refined grains, but fruits and vegetables are better than grains. Evolutionarily, we got our carbohydrate from fruits and vegetables and very little from grains. The agricultural revolution changed that. Most of our carbohydrate came from grains. We ate less and less fresh fruits and vegetables, and more and more fatty meats.

JB: I've had several recent discussions with Dr. Simin Liu from Harvard, who has been doing quite a bit of work on diet and its relationship to type 2 diabetes. He commented that we often focus a lot of our attention on the altered macronutrient intake associated with insulin resistance and hyperinsulinemia, but that there are also a lot of phytonutrients in fresh fruit and vegetable-rich, minimally-processed, grain-rich diets that probably have beneficial effects on insulin signaling. Is it your sense that these complex constituents also play an advantageous role in the Paleo Diet?

Effect of Neolithic Foods in the Diet

LC: Yes. Simin Liu is a close colleague of Jenny Brand-Miller, a coauthor on one of our papers on acne vulgaris. She is the author of the International Table of Glycemic Indices. I've had numerous conversations with Jenny and David Ludwig at Harvard. I'm absolutely on board with that. I don't think diseases of insulin resistance have just one cause; they're multifactorial. Phytochemicals, fiber, minerals, vitamins, omega 3 fatty acids are all involved. High glycemic-load carbohydrates are one of the major factors, but omega 3 fatty acids also play a dominant role. It's a lot like a symphony orchestra. We need to listen to all of the instruments; we need to listen to the magic of the music rather than picking out single elements. That's really the beauty of the paleolithic concept; it's an organizing template that allows us to realize how all of these multiple elements come together. As I pointed out in my book and also in an article that we are preparing right now for the American Journal of Clinical Nutrition, these Neolithic foods that have been increasingly introduced in our diet have altered seven major areas that influence our health and well being. Phytochemicals, vitamins, and minerals comprise one area. The nutrient-density (content) of cereal grains is a joke compared to fresh fruits, vegetables, lean meats and seafood.

JB: The pendulum of nutrition swings back and forth. I've been in this field for 30 years and I'm in the third cycle of harispendulum swinging as it relates to health, diet, and macronutrients. We can name many personalities associated with different diet approaches. We've got Pritikin, Ornish, Atkins, and Sears. There are many different persuasions as to how to prevent degenerative disease. We have everything from the very high complex carbohydrate, unrefined diet, which is modest in protein (about 15 calorie percent) up through suggested amounts as high as 50 percent protein. Each individual claims his diet approach is the one that will create lowered incidence of the major degenerative diseases. What is your take on all of this?

Charismatic Individuals and Various Diet Plans

LC: In my search for answers, I've seen many charismatic individuals who advocated different types of diets come and go, from Paul Bragg in the 1950s to Jack LaLanne, to Frances Moore Lappe (Diet for a Small Planet), on through Atkins, Sears, and Ornish. These diets are dependent on the charisma of a single individual interpreting the data. Rather, the beauty of the Paleo Diet concept is that it requires no charismatic individual; it simply requires an organizing template. The most powerful organizing template

in all of biology is evolution through natural selection; it is the governing paradigm for all biological and medical sciences. All medical and biological sciences are determined by evolution through natural selection. We are all organisms that have been created through evolution via natural selection. The trail, or the clues, have been left behind, not by a charismatic individual, not necessarily by dietary interventions, but by examination of who we are and where we came from. Long after I am dead and gone, the concept of applying evolution and natural selection to nutrition, diet, and health will continue, because it is the correct organizing paradigm. Barry Sears doesn't organize diet and nutrition; genes organize diet and nutrition. By uncovering these elements, we will be able to determine the optimal human diet.

JB: That's a very compelling argument, one I am going to remember in the future. We will be privileged to have you as a keynote speaker at our 11th International Symposium on Functional Medicine in May. Those who have listened to you in this edition of Functional Medicine Update will have a greater opportunity in Vancouver to hear much more. Thank you for your hard work and for sharing it with us today.

LC: Thank you, Jeff. I'm looking forward to meeting you and presenting at the May symposium.

We thank Dr. Cordain for an informative and eloquent presentation concerning some dietary modifications and their impact on insulin signaling. He made a complex topic easier to understand.

At the end of the interview, we talked briefly about the role various phytochemicals and plant foods might have on insulin. I would like to revisit that subject in light of the recent body of research on some of these substances.

Hydroxychalcone Derived from Cinnamon Functions as a Mimetic for Insulin in 3T3-L1 Adipocytes

One class of substances receiving quite a bit of attention are the hydroxychalcone derivatives from cinnamon. This was first discussed by Dr. Richard Anderson in some preliminary papers looking at cinnamon's effect on insulin sensitivity. There is an interesting paper that appeared in the *Journal of the American College of Nutrition* by Dr. Anderson from the Human Nutrition Center in Beltsville, MD and his colleagues, Drs. Karalee Jarvill-Taylor and Donald Graves, from the Department of Biochemistry at Iowa State University.[14] Based upon observational studies and animal work on the role of cinnamon in insulin sensitivity, this group performed experiments with the cinnamon methylhydroxychalcone polymer and insulin with regard to glucose uptake, glycogen synthesis, phosphatidylinositol-3-kinase dependency, glycogen synthase activation, and glycogen synthase kinase-3β activity.

It was found that the methylhydroxychalcone fraction appeared to have important insulin mimetic effects in adipocyte cells. Insulin mimetic means insulin-like. It seemed to participate in the same type of influence on gene expression signaling and on glucose transport as insulin itself. These investigators conclude that the results demonstrate that the methylhydroxychalcone derivative from cinnamon is an effective mimetic of insulin and therefore may be useful in the management of insulin resistance and in the study of the pathways leading to glucose utilization in cells.

A number of other papers have followed up on this, examining the effect of cinnamon fractions on insulin

signaling by certain molecular biological probes—various phosphorylase enzymes and receptor kinase enzymes involved in insulin sensitivity. There is a nice paper in *Hormone Research* discussing that various cinnamon compounds derived from the hydroxychalcone fraction are involved with insulin-like effects, and the influence they have on specific gene family receptor signaling, indicative of an insulin-like mimetic effect.[15]

We are beginning to see some positive influences that various phytochemicals have on insulin-like mediated glucose transport and gene expression. Some studies suggest that 1 gm or 1000 mg of cinnamon containing hydroxychalcone in concentrated form, is capable of greatly improving the areas under the curve after a glucose challenge, demonstrating insulin-stimulating and sensitizing effects. It also appears to bear out in human intervention trials in individuals who have various types of insulin insensitivity or insulin resistance.

This is an exciting part of the story showing that there are undoubtedly many different substances found in plants that participate in insulin sensitization. This is discussed in an abstract in the FASEB Journal.[16] A paper in Hormone Research supports these observations and discusses insulin action from cinnamon extract.

Green Tea Epigallocatechin Gallate and Insulin Biological Activity

In a review in the *Journal of Agricultural Food Chemistry*, investigators discussed examination of insulin-like biological activity of culinary and medicinal plant extracts and determined that cinnamon was the most bioactive product.[18] Epigallocatechin gallate, in green and black tea, was also high on the list. It is well known that tea enhances insulin activity. This is discussed in an article in the *Journal of Agricultural Food Chemistry*.[19]

We are advancing the understanding of phytochemicals and the physiological mechanisms by which food can influence insulin and insulin reactivity. The cinnamon story is interesting, although it does not argue for consuming cinnamon rolls on a frequent basis. I do not think we can justify the amount of cinnamon in white-flour bakery products to overcome their glycemic load.

Regarding green tea epigallocatechin gallate, or EGCG, there are a number of papers that discuss its beneficial effect on insulin sensitivity. One article appeared in the journal, *Experimental Molecular Medicine*. EGCG was seen to suppress pancreatic β cell injury due to oxidative stress and improve insulin secretion.[20] There are beneficial effects of tea catechins on improving glucose transport and reducing the risk to obesity. This is discussed in an article in the *International Journal of Obesity*.[21]

The point I am trying to make is that are a variety of phytochemicals from different foods and culinary spices that may play favorable roles in helping sensitize the cell signaling process related to insulin. That may also constitute the value of a natural, highly unprocessed plant food-rich diet. These phytochemicals are not found in animal products. I want to emphasize that the complex diet—a mixture of animal and vegetable products of the right type—is undoubtedly what the anthropological history and the emerging physiological story appears to argue for.

Lipoic Acid and Insulin Regulation

How we view diet and its interrelationship to insulin sensitivity is a fascinating chapter in the emerging understanding of the important role that diet plays in medicine. We began with what Linus Pauling might have called an orthomolecular, α -lipoic acid, as a useful agent for improving insulin sensitivity and perhaps in the treatment of certain forms of diabetic neuropathy, when given in therapeutic doses from 600-1200 mg per day. Everyone jumped on the lipoic acid bandwagon as if it was the universal management tool for insulin resistance.

There are many interesting papers on the role of supplemental α -lipoic acid in type 2 diabetes and improvement of the insulin response. One is an article that appeared in *Free Radical Biology & Medicine*.[22] A clinical intervention, placebo-controlled trial demonstrated that 1200 mg of lipoic acid was capable of improving insulin response and managing glucose response in type 2 diabetics.

People started to look at α -lipoid acid as the nutrient to treat diabetes. However, we should be looking at α -lipoic acid, not by itself, but as part of a complex family of nutrients involved in the reduction/oxidation control of beta cell function, insulin sensitivity, and glucose transport. Unfortunately, we often fall into the pharmacological model, thinking that if we can find an effective nutrient, that it is "the drug" for insulin management. Rather, we need to view it as part of a complex milieu of interacting variables from a whole-foods diet, and proper physiology that ultimately regulates cell response at the genotypic level, the so-called nutrigenomic level that controls the phenotype in things such as blood sugar normalization.

Certainly, there appears to be a role for α -lipoic acid. It is probably best when included in an overall dietary intervention program, using all the things Dr. Cordain talked about. We still have to eat nutrients; we still have to consume macronutrients and calories. We cannot live on α -lipoic acid alone. We need to put α -lipoic acid in the proper context, the same as vitamins C and E. We know that vitamin E will improve insulin sensitivity. That is not because of vitamin E alone, but as a factor in the presence of other nutrients such as magnesium, vitamin C, calcium, polyunsaturated fatty acids, and other phytonutrients I discussed. All of these work together to give rise to improved insulin response.

What seems to be emerging is the concept that the less processed the diet and the more color and texture it has, the more likely it will deliver substances that help to regulate gene expression in a positive way. Dr. Cordain, Boyd Eaton, and others are doing remarkable work, examining the anthropology and history of the human diet and its relationship to function, and there is significant work being done in nutrigenomics and the physiology of glucose control. These seem to converge into a single story—lower processed foods, higher fiber, phytochemicals, less partially hydrogenated vegetable oils and saturated fats, and more of the antioxidant-rich nutrients. All of these are helping to move us in the right direction.

Other Foods/Spices and Insulin Regulation

I find the cinnamon story to be interesting. If a culinary spice containing a family of substances called hydroxychalcones can positively influence insulin signaling, there may be many other substances derived from different foods and spice products that, as we study them, will demonstrate positive effects on insulin signaling. One of those is bitter melon (*Momordica charantia*) which has been historically used as a concentrate to help improve insulin regulation.[23]

There are plants that have been historically used in equatorial West Africa for normalization of blood

sugar. Plants from Amazonia in South America have also been used by indigenous cultures to regulate glucose and treat what we call diabetes.[24] There are hundreds of compounds and medicinal herbs found in various foods and spices now being discovered that undoubtedly play roles in modulating the complex signaling process of insulin, such as the PPARs.

We will be learning much more about this as the science unfolds, as well as more about the history of diets, what phytochemicals they contain, and how that relates to some of the ongoing clinical intervention trials. Rather than thinking we need only a single nutrient to treat a disease called diabetes, we should be talking about the complex array of substances from the diet and lifestyle, including exercise. When those factors are combined in the right proportion for that person's genotype, they result in an outcome called proper glucoregulation. When that occurs, glycosylation decreases, insulin signaling at the gene level decreases, inflammatory mediators decrease, as well as some of the secondary risk factors such as cell proliferation that Dr. Cordain described. It is not just a single problem related to diabetes in and of itself.

When we tie this together with the extraordinary Clinician of the Month interview we had last month, in which we talked about insulin and cancer with Dr. Barry Boyd, there is a lot more mileage to be gained as we move into our studies for the symposium.

Thanks for being with us. I hope you have received some "news to use" this month about diet and the modification of insulin signaling.

Bibliography

1 Podell RN. Understanding the transition from alternative medicine to mainstream science: the homocysteine theory of heart disease and the crucial role of effective mentoring. Med Hypotheses. 2003;61(3):340-345.

2 Eckel RH. A new look at dietary protein in diabetes. Am J Clin Nutr. 2003;78:671-672.

3 Gannon MC, Nuttall FQ, Saeed A, Jordan K, Hoover H. An increase in dietary protein improves the blood glucose response in persons with type 2 diabetes. Am J Clin Nutr. 2003;78:734-741.

4 Daly M. Sugars, insulin sensitivity, and the postprandial state. Am J Clin Nutr. 2003;78(suppl):865S-872S.

5 Jenkins DJ, Kendall CW, Marchie A, et al. Type 2 diabetes and the vegetarian diet. Am J Clin Nutr. 2003;78(suppl):610S-616S.

6 Sabatè J. The contribution of vegetarian diets to health and disease: a paradigm shift? Am J Clin Nutr. 2003;78(suppl):502S-507S.

7 Dattilo AM, Miguel SG. Chromium in health and disease. Nutr Today. 2003;38(4):121-133.

8 Nesto RW, Brunzell JD, Plutzky J. The clock is ticking&ldots;attacking the metabolic syndrome to

reduce atherosclerotic risk. Cardiol Rev. 2002;19(13suppl):2-16.

9 McCarty MF. A paradox resolved: the postprandial model of insulin resistance explains why gynoid adiposity appears to be protective. Med Hypotheses. 2003;61(2):173-176.

10 Eaton SB, Konner M. Paleolithic nutrition. A consideration of its nature and current implications. N Engl J Med. 1985;312(5):283-289.

11 Cordain L, Lindeberg S, Hurtado M, Hill K, Eaton SB, Brand-Miller J. Acne vulgaris: a disease of Western civilization. Arch Dermatol. 2002;138(12):1584-1590.

12 Cordain L, Eades MR, Eades MD. Hyperinsulinemic diseases of civilization: more than just Syndrome X. Comp Biochem Physiol A Mol Integr Physiol. 2003;136(1):95-112.

13 Cordain L, Miller JB, Eaton SB, Mann N, Holt SHA, Speth JD. Plant-animal subsistence ratios and macronutrient energy estimations in worldwide hunter-gatherer diets. Am J Clin Nutr 2000,71(3):682-692.

14 Jarvill-Taylor KJ, Anderson RA, Graves DJ. A hydroxychalcone derived from cinnamon functions as a mimetic for insulin in 3T3-L1 adipocytes. J Am Coll Nutr. 2001;20(4):327-336.

15 Imparl-Radosevich J, Deas S, Polansky MM, et al. Regulation of PTP-1 and insulin receptor kinase by fractions from cinnamon: implications for cinnamon regulation of insulin signalling. Horm Res. 1998;50:177-182.

16 Maber MA, Sokis LM. Cinnamon consumption may enhance insulin action in vivo. FASEB J. 2001;15:A992.

17 Berrio LF, Polansky MM, Anderson RA. Insulin activity: stimulatory effects of cinnamon and Brewer's Yeast as influenced by albumin. Horm Res. 1992;37:225-229.

18 Broadhurst CL, Polansky MM, Anderson RA. Insulin-like biological activity of culinary and medicinal plant aqueous extracts in vitro. J Agric Food Chem. 2000;48:849-852

19 Anderson RA, Polansky MM. Tea enhances insulin activity. J Agric Food Chem. 2002;50:7182-7186.

20 Han MK. Epigallocatechin gallate, a constituent of green tea, suppresses cytokine-induced pancreatic b -cell damage. Exp Mol Med. 2003;35(2):136-139.

21 Murase T, Nagasawa A. Suzuki J, Hase T, Tokimitsu I. Beneficial effects of tea catechins on diet-induced obesity: stimulation of lipid catabolism in the liver. Int J Obesity. 2002;26:1459-1464.

22 Jacob S, Ruus P, Hermann R, et al. Oral administration of RAC-a -lipoic acid modulates insulin sensitivity in patients with type-2 diabetes mellitus: a placebo-controlled pilot trial. Free Rad Biol Med. 1999;27(3/4):309-314.

23 Chen Q, Chan LL, Li ET. Bitter melon (Momordica charantia) reduces adiposity, lowers serum insulin and normalizes glucose tolerance in rats fed a high fat diet. J Nutr. 2003;133(4):1088-1093.

24 Schwontkowski D. Herbal treasures from the Amazon. Healthy & Natural J. 1994p>