February 2001 | Diana Schwarzbein, MD -The Endocrinology Institute of Santa Barbara

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Welcome to *Functional Medicine Update* for February 2001. This year we will focus on neuroendocrinology, both in our *FMU* presentations and in our upcoming symposium. I remind you to make plans to attend the Eighth International Symposium on Functional Medicine, which will be held in Vancouver, British Columbia, May 22-26 at the Westin Bayshore Marina resort, right outside Stanley Park. Our biochemistry and clinical nutrition training program is all put together, and our plenary speakers are arranged. I believe it is going to be a tremendous program. We will soon send you a brochure as a reminder.

This month's *FMU* Clinician of the Month will take the complex topic of functional endocrinology and guide us into clinical management programs in patients, particularly female patients, with central adiposity, hormone imbalances, sugar cravings, and cardiovascular risk. These patients may show signs of imbalances in progesterone/estrogen/testosterone. I think you will find this interview informative.

Pharmacogenomics and Cancer Treatment

Before we get to that interview, I want to lay some groundwork by going back to the cornerstone of functional medicine, which is functional genomics. That interesting term redefines what Dr. Roger Williams called biochemical individuality and Dr. Linus Pauling called molecular medicine. In the early 21st century we talk about the gene diversity genotype/phenotype connection to illness.

A recent paper in the *New England Journal of Medicine* helps us understand the rapidly unfolding evolution of medicine. Some medical historians now say the next 10 years, from 2000 to 2010, will be the most dramatic years in the evolution of health care and medicine in the history of the development of formalized medicine.

Functional Medicine and Predicting Response to Chemotherapy

An interesting editorial, titled "Inactivation of the DNA-Repair Gene MGMT and the Clinical Response of Gliomas to Alkylating Agents," accompanies a recent paper in the *New England Journal of Medicine* The editorial focuses on the response of patients with gliomas to specific nitrosourea chemotherapeutic agents.

I want to provide some background to explain why I think this information signals a new chapter in

medicine and its relationship to functional medicine, because the functional medicine connection to patients with gliomas may not immediately be clear. Traditionally, cancer treatment has been selected on the basis of tumor type, pathological features, clinical stage, patient's age, and other nonmolecular considerations. It has been an art as much as a science. Generally, we have developed a fatalism based on the pigeonholing of patients into given categories. Some will have dramatic, positive response to a therapy, and others will not. We generally accept this as the luck of the draw. Oncologists have been able to do little to predict the way patients will respond, which therefore, is viewed as a matter of luck, like the result of a coin toss. It is possible, in some cases, to predict treatment response based on pharmacogenetic methods now being developed—ways of looking at unique biochemical and genetic response to the phenotypic outcome from a gene response modifier.

Pharmacogenomics and Pharmacogenetics

Pharmacogenomics and pharmacogenetics represent the study of a large number of genes that influence drug activity, toxicity, and metabolism. This combined field provides an opportunity to tailor specific pharmacological therapies and eliminate many uncertainties. The *New England Journal of Medicine* paper goes a step further. Much of what we have been discussing in terms of functional genomics relates to gene expression in relation to protein as ultimately coming through messenger RNA. In this case, the study is about epigenetic effects that occur after the gene has been transcribed and translated and a protein has been formed. We want to discuss this facet of the gene expression story. Gene expression includes not merely the synthesis of a unique protein, but also its post-translational modification. Many things, including glycosylation, phosphorylation, sulfation, and oxidation, can occur after proteins are synthesized and play a role in its physiological activity.

The specific epigenetic event to which I refer in this article is methylation. This could be considered a chicken-and-egg argument, if we ask what controls methylation. It has its own genes for control. Therefore, some things that can control genetic expression of methylation can in turn control epigenetic methylation of nucleic acids that control function. Various modifiable factors interact on a number of levels with genetic hard-wiring and environmental modulators, producing outcome differences.

Understanding Variations in Treatment Outcomes

Esteller, the author of the *New England Journal of Medicine* article about gliomas and nitrosourea alkylating agents in chemotherapy, pointed out that some gliomas are resistant to nitrosourea alkylating agents. Carmustine, a very common chemotherapeutic agent, kills by alkylating the O^6 position of guanine in the DNA and forming crosslinks adjacent strands of DNA. That is how it works as an alkylating agent and as a chemotherapeutic agent. Wide variations have been found in response to this drug in different patients, and those variations contribute to the different treatment outcomes. A DNA repair enzyme called O^6-methylguanine-DNA methyltransferase (MGMT), however, reverses the alkylation reaction and prevents formation of these crosslinks. This enzyme dealkyates the damaged DNA thereby repairing it. The net result is to interfere with the chemotherapeutic potential of carmustine.

We now know wide variations exist in the expression of this MGMT enzyme. They are found within and among different types of tumors. Not all patients are the same in the way they methylate these damaged DNAs. This is an epigenetic effect.

Post-Translational Methylation Effects on Chemotherapy Outcome

Cells convert the information within their DNA to protein via the intermediate messenger RNA. If the transcription of DNA to mRNA is prevented, no protein is made. A common method cells use to prevent transcription is to methylate specific guanine residues within a particular gene. We might ask if those who are nonresponsive to the alkylating chemotherapeutic agent carmustine are individuals who have increased or decreased activity of MGMT due to methylation effects that influence the ability of cells to synthesize the active enzyme. Individuals lacking MGMT would be likely to respond to chemotherapy with carmustine. This is an interesting problem.

The Esteller et. al. paper considers this problem. It has been proposed that the methylation of the MGMT promoter region, with consequent transcriptional silencing of the gene, accounts for the variation in DNA repair. The Esteller study found 12 of 19 patients with methylated promoters in their tumors had partial or complete response to carmustine, whereas only 1 in 28 patients with an unmethylated promoter had a response. The significance between the two groups was $P<0.001$. This study has significant clinical implications. If we rely on "the luck of the draw" without knowing anything about the MGMT promoter methylation effects in these patients, we would simply say there were atypical or bad responders and good responders. We would have no way of predicting outcome. By knowing something about the methylation promoter region in these MGMT polymorphs, we are much better able to predict which ones will be responders. Twelve of 19 patients with the methylated promoters had a partial or complete remission, versus only 1 of 28 in those who did not have that genetic tendency.

Epigenetic Manipulators of Outcome and Function

This study has a number of implications. It suggests there may be epigenetic as well as genetic manipulators of outcome and function. Methylation, which is controlled in part through a series of methylating enzymes, depends on the activity and proper function of the methyltetrahydrofolate cycle. That folic acid/B12/B6/betaine cycle relates to the formation of active methyl groups that can be used as donors for these methylation reactions. You might wonder if individuals who are insufficient in folate/B12/B6 are more susceptible to chemical carcinogens. The answer is yes. Are individuals who are folate/B12/B6-insufficient less responsive to carmustine or other nitrosyl alkylating reagents involved in chemotherapy? That has not been studied yet, but it is another interesting question.

This particular study suggests that polymorphism in the methylation of these promoter regions in DNA is associated with the MGMT enzyme. Individuals who are poor methylators due to insufficiencies of folate/B12/B6, might be unable to silence those genes related to specific functions that lead to poorer response to this specific type of chemotherapy. What is emerging is a molecular explanation in individuals who might benefit from specific nutritional support to augment or optimize the ability to respond to specific chemotherapeutic drugs. This is true molecular medicine, as Dr. Linus Pauling suggested back in 1949.

"Omic" Research

We are looking at both genetic and epigenetic effects and how they influence outcome. We are doing so by once again examining genetic uniquenesses in individuals and tying it together with modifiable factors. This leads to what is called "omic" research. You might think of pharmagenomics or proteomics

or kinomics or metabolomics as the tying together of specific processes in physiology to the genetic characteristics of the individual—the genotype/phenotype connection, moving also through epigenetic effects.

Neurogenesis in the Adult Brain

In discussing women's health-related issues of neuroimmunology and neuroendocrinology, we should also consider the brain, because we are going to be dealing with neuroendocrinology. In relation to the brain and the central nervous system, most of us were taught that, once neuronal cells were formed in early childhood, no more could be produced. We had our allotment for life; they would not reproduce, replicate, or repair themselves. I recall the old adage I learned during college that if you had a few too many beers on a Friday or Saturday night, you lost so many million brain cells that would never come back. One metered out how many brain cells one was willing to lose over the course of a lifetime of partying. There has been that kind of determinism about the central nervous system.

Everything in anatomy and physiology is in a state of change as we regard them from new perspectives in medicine. The determinism of the absolute number of neurons throughout adult life is also under review. A paper on this topic by Charles Gross appeared in *Nature Reviews/Neuroscience.* It is titled "Neurogenesis in the Adult Brain: Death of a Dogma." This article argues once again that the brain has much greater plasticity, adaptability, recovery ability, and resilience as an organ than we previously ascribed to it through our more deterministic view of death and disease.

Resilience of the Human Brain According to Dr. Gross:

> "Until very recently, a central dogma of neuroscience has been that new neurons are not added to the adult mammalian brain. For more than 100 years it has been assumed that neurogenesis, or the production of new neurons, occurs only during development and stops before puberty. Indeed, there are few views of the brain that have persisted for so long with so little successful challenge."

Things did start to change, however, in the early 1960s, when Joseph Altman began publishing a series of papers in which he reported there was an uptake of radioactive thymidine in the brain in adult animals, suggesting the evidence for adding new neurons. This phenomenon was found in both young and adult animals, occurring in the neocortex, the dentate gyrus, and the olfactory bulb. He also reported new neurons in the neocortex and elsewhere in the adult cat, showing cross-species similarity.

"Although published in the most prestigious journals of the time, such as the *Journal of Comparative Neurology, Science* and *Nature,* these findings were ignored or dismissed as unimportant for over two decades." It did not fit into the central dogma of the time and people said it couldn't be, so they didn't look at the results.

Electron Microscopy Studies Provide Evidence

"Fifteen years after Altman's first report, direct support for his claim of adult neurogenesis came from a series of electron microscopy studies by Michael Kaplan and his coauthors. First, they showed that [^{3}H]-thymidine-labeled cells in the dentate gyrus and olfactory bulb of adult rats have the ultra-structural characteristics of neurons, such as dendrites and synapses, but not of astrocytes or oligodendrocytes. Then Kaplan reported autoradiographic and ultrastructural evidence for a few new neurons in the cerebral cortex of adult rats, confirming Altman's earlier claims.

"Again, as in Altman's case, publication in prestigious and rigorously reviewed journals, such as *Science,* the *Journal of Comparative Neurology* and the *Journal of Neuroscience*…"

The Beginnings of Neuroscience

Unfortunately, however, as you might expect, since Kaplan was not a well-known figure, he did not make a dent in the dogma by the publication of these papers.

If we look at other data, we see that many other investigators entered this field and published similar work in the 1970s and 1980s, indicating neurogenesis in different portions of adult animal brains. Their work seemed to confirm that regeneration was taking place. We now recognize that every day thousands of new neurons are added to the mammalian brain. "Although the new neurons are miniscule in proportion to the total population, their continual addition over a lifetime implies considerable structural change." Our brain is plastic. It is regenerating itself. "The magnitude and ubiquity of adult neurogenesis across vertebrates suggests that it is functionally significant and not merely a vestige of development." This flies in the face of everything we learned about too many beers on Friday night causing irreplaceable loss of neurons.

"The idea that new neurons are not added to the brains of adult mammals dates back to the neuron doctrine and the origins of modern neuroscience at the end of the 19th century. The tenacious persistence of this dogma in the face of empirical contradiction and its relatively recent demise illustrates, among other things, the strength of tradition and the difficulty that unknown and junior scientists have in challenging such traditions. It also suggests the necessity for new ideas to arise in a supportive matrix if they are to survive, and under scores the importance of new techniques."

Neuronal Development and Changes in the Way We Think

"It should be stressed that the actual number of adult-generated neurons is a small proportion of the total population of neurons. But the existence of adult-generated neurons in the hippocampus (and probably elsewhere), and the possibility that these cells may function in learning and memory offer new mechanisms for information storage in the brain. It may be that learning and memory involve the development of entirely new circuits with new and previously unused elements as well as the modulation of older circuits and connections." Our way of thinking, as we grow older, may actually change, due to the changes in neuronal development and the addition of new neurons, which may have different functions over the course of a lifetime.

"Use It or Lose It" Theory Applied to Genomics

Neurogenicity is a profound example of the plasticity and organizational structure change that occur

throughout the life process, the rhythms that shape our lives. These changes impacting on a pleuripotential genome produce an outcome that is us, as individuals. It varies throughout the course of life and can be regenerated, revitalized, and restored, with new resilience added, by practicing the right things. This is true even of the central nervous system.

It is the old "use it or lose it" theory, set in a different context, the parlance of 21st century genomics.

Inflammation and Coronary Artery Disease

Let us move to hormone- and insulin-related phenomena in the context of neuroendocrinology. One of the things we will discuss with our Clinician of the Month is the relative role of insulin and glucose in wide-ranging, organ-specific, pathological events, including coronary artery disease. Coronary artery disease is more than just a cholesterol problem. It is related to a series of interconnecting events that increase the initiation and progression of atheromas.

For several years in *FMU* we have been discussing the role of chronic inflammatory mediators in the etiology of coronary artery disease. Rudolph Virchow, the German physiologist, was the first to propose that heart disease and coronary artery disease were inflammatory conditions, like lesions or abrasions, with similar types of processes involved in their initiation. Over the past decade, we have come to believe that atherosclerosis is, in fact, related to an inflammatory condition, and serum levels of markers of inflammation can even be used to predict the risk of coronary disease.

High-Sensitivity CRP Elevations and Cardiovascular Disease

In studying extended risk factors for cardiovascular disease, Dr. Paul Ridker at Harvard Medical School showed the importance of CRP elevations easily monitored with newer, high-sensitivity assays. This was not just normal C-reactive protein, but the higher-sensitivity techniques that show even marginal elevations are associated with increased risk and incidence of heart disease.

Two papers appeared recently in the *New England Journal of Medicine* that confirm and extend the concept that inflammation and heart disease are interrelated. One is titled "Markers of Myocardial Damage and Inflammation in Relation to Long-term Mortality in Unstable Coronary Artery Disease." The authors of this article consider the risk of coronary death in individuals who have varying degrees of inflammatory markers in their plasma. Another paper is titled "Lipoprotein-Associated Phospholipase A_2 as an Independent Predictor of Coronary Heart Disease." In both papers, investigators found that elevated levels of inflammatory mediators in biological fluids are associated with increasing risk of disease or, in the first paper, death. There is clear evidence that factors that increase the chronic inflammatory modulation may also be related to heart disease as cholesterol-independent risk factors.

The Inflammatory Role of Adipose Tissue

An interesting figure appears in the editorial that accompanies these two papers. The editorial is titled "Inflammatory Markers of Coronary Risk." The figure, titled "Sources of Inflammatory Markers and Cytokines," points out that these inflammatory mediators are produced by a variety of tissues, including the vessel wall, circulating macrophages, and the adipose tissue. (We will discuss adipose tissue as a source of inflammatory mediators as we get into the insulin connection to heart disease risk.) Adipose

tissue also elaborates tumor necrosis factor a and interleukin 1b . These substances then influence liver Kupffer cells, the embedded white cells in the liver, to produce their reactive molecules, C-reactive protein, fibrinogen, and serum amyloid a , which then go into plasma and are associated with systemic inflammation risk.

What this figure does not show that I think is an omission, is the contribution of the gastrointestinal tract, the gut associated lymphoid tissue (GALT), to the overall body burden of inflammatory mediators. It is interesting that they do not include the GI tract in the sources of inflammatory messages, because a number of studies now show that the GALT is an important source of bacterial lipopolysaccharides. These lipopolysaccharides initiate these particular inflammatory mediators and influence the Kupffer cell production of inflammatory messengers such as C-reactive protein, fibrinogen, and serum amyloid a . This combination adds to the total load and the upregulation of the inflammatory system. Chronic infection can lead to chronic inflammation, as can exposure to toxins, gut endobiosis; and situations related to injury, through ischemic insults that cause increased production of inflammatory mediators, insulin resistance/hyperinsulinemia, and obesity.

Insulin Resistance and VAT

The elevated insulin which is seen in insulin resistance is also associated with the increased production of proinflammatory mediators. As I mentioned earlier, this also relates to the role of visceral adipose tissue (VAT) that we often associate with insulin resistance and hyperinsulinemia. We are beginning to understand that coronary artery disease risk is associated with inflammatory mediators that may be amplified in part by insulin resistance/hyperinsulinemia and its relationship to metabolic obesity, or the accumulation of central body fat around the waist and hips, the so-called "apple-shaped body."

This association helps us appreciate the importance of a comprehensive management program in reducing the greatest risk of death—coronary disease—in our population. Focusing solely on cholesterol may be only part of the story we need to heed in developing a comprehensive health promotion program for an individual.

Niacin's Effect on Lipid and Lipoprotein Levels in Diabetes

Niacin (nicotinic acid) is one of the specific therapeutic agents that have been known to influence cholesterol and heart disease risk. For many years we have known that therapeutic doses of nicotinic acid—not niacinamide, but nicotinic acid itself—serve as a useful anti-hypercholesterolemic agent. Therapeutic doses are quite high—in the range of 2000 to 3000 mg per day, generally upward of 3000 mg a day. For most people, just the thought of that much niacin causes severe flushing. You can imagine the flushing that results from a first dose of 3000 mg a day of niacin. It is generally not considered useful to administer two daily doses of 1500 mg each of niacin to an individual who has never been on it.

A protocol has been developed to build a patient’s tolerance to high levels of niacin. That protocol involves giving a baby aspirin about 20 minutes before administering the niacin, to deactivate the histamine response. Over the course of two to three weeks of giving the baby aspirin before giving niacin, the body eventually learns to accommodate the niacin. The patient will not flush, so he or she won’t need the baby aspirin any longer. That is a clinical insight for using nicotinic acid at higher doses in patients without producing serious flushing reactions.

Niacin and Diabetes

A recent paper in the *Journal of the American Medical Association* indicates that lipid-modifying doses of niacin can be safely used in patients and that it may also help to improve insulin sensitivity in diabetic patients. Diabetic patients who have lipid abnormalities experience increased HDL levels from niacin treatment, as well as lowered atherogenic LDL levels, reduced triglycerides. This is an interesting outcome from the connection between nicotinic acid, cholesterol, and insulin resistance, which is another risk factor for coronary artery disease.

In nicotinic acid-treated patients, administering high doses of niacin resulted in modest increases in glucose levels in participants with and without diabetes. Levels of hemoglobin A1C, however, were unchanged from baseline to follow-up in the diabetes patients treated, and insulin sensitivity appeared to improve. Therefore, there is no significant difference in the diabetic condition with or without niacin therapy. These would seem to be interrelated variables. There is the cholesterol connection with increased LDL cholesterol biosynthesis and its interrelationship to insulin and to glucagon, cortisol, and epinephrine, and this web of intervening messenger molecules including the proinflammatory mediators, that all somehow regulate arterial dynamics, macrophage monocyte conversion to foam cells, and atherogenesis.

Food as Information—Whole Grains Lower Women's Risk of Ischemic Stroke

Foods contain a number of principles other than just nicotinic acid that can be used in nutritional pharmacology. Many substances in foods have effects on the arterial process—the vasodynamics, hormonal balance, endocrine messaging, and neuroendocrine connections. Food contains a complex array of information molecules. It is a different way to define diet, but in a sense food is information. It provides instructions to receptor sites, which modify the genetic message and create different phenotypic outcomes. Thinking of food as information implies increased responsibility for the way we eat. What information do we want to provide to our genetic encyclopedia? What do we want to create in terms of what is read out of that encyclopedia?

One study found quite a difference between whole foods that contain a vast array of micronutrients and highly processed foods from which many of the colored compounds have been removed. Food processors consider the exosperm and fiber components of grains to be the flotsam and jetsam of foods. Removing them leaves behind the principle of carbohydrate alone. There is a big difference between the two types of food.

Whole Grains versus Refined Flour Products

When we refer to carbohydrate, we could be talking about carbohydrate with all the residual compounds that were synthesized by the whole plant in the seed of wheat, corn, or rice. Or we might be referring to the white flour starch derivative from which the husk, hull, and germ have been removed. That difference is described in a recent paper in the *Journal of the American Medical Association.* In this paper, titled "Whole Grain Consumption and Risk of Ischemic Stroke in Women," the authors looked at the intake of whole grain foods as compared to white flour products to determine if there was any difference in the risk of ischemic stroke. They found consumption of whole-grain foods was associated with a statistically highly significant reduction in the risk of ischemic stroke, independent of known cardiovascular disease

factors in these women.

These prospective data support the contention that the higher intake of plant-derived phytonutrients in unrefined grains is useful in modulating function and reducing the risk of degenerative disease. We need to be cautious in discussing protein, carbohydrate, and fat to be sure we are defining our principles carefully. Whole-grain, starch-rich products may be very different from carbohydrate-only white starch types of macronutrient diets. Removing those colored compounds, the flotsam and jetsam, fibrous materials, and micronutrients and just adding back a few of nutrients to prevent deficiency diseases such as beriberi and pellagra may influence gene expression in an entirely different way.

This distinctions clinically important. We see published data comparing the value of a diet with a particular ratio of carbohydrate/protein/fat to a diet with a different ratio. Should the carbohydrate/protein/fat ratio be 60/20/20, 40/30/30 or 50/30/20? Although various ratios are suggested, it is far more important to consider the form of these various nutrients and whether they also contain the micronutrients, fiber, and other phytonutrients, issues that often are not discussed in a study.

The Role of Oxidation in Atherosclerosis

We know little about the effects of the diets we are consuming today, which contain oxidized lipids, partially hydrogenated trans-containing vegetable oils, heavy metals that may be prooxidants, and food antigens from genetic inbreeding. All of these factors can have an impact on the immune system, the cell signaling system, the GALT, and the circulating white cells. They can alter the way the body responds to the diet. In other words, the information the body is getting from the diet is translated less as a friend and more as an enemy invader. These perceived enemy substances produce nonspecific, generalized immune upregulation. Although this upregulation may not lead to what we call frank allergy, it may cause a low-grade immunological activation.

Increased activation and the release of reactive molecules by white cells can lead to what is called the Klebanoff reaction. This refers to the myeloperoxidase-generated production of chemical oxidants, the chemical warfare agents from white cells. These oxidants, hypochlorites, react chemically to form substances like superoxide, which can be dismutated into hydroxyl radical and hydrogen peroxide. These substances are prooxidants. Therefore, upregulation of the immune system produces more oxidants. More oxidants lead to more potential oxidative injury to LDL, lipoprotein, and cholesterol, which then makes it more of a mutagenic agent and more capable of transforming cells into these atherogenic foam cells.

The Web of Function in Inflammation

An article in *Free Radical Biology & Medicine* looked at atherosclerosis as a chronic inflammatory process in which oxidation within the artery wall is implicated in the pathogenesis of the disease. The authors examined the connection between this process and the release of these oxidants by mononuclear phagocytes when they are activated by a variety of agents, including such initiators as chronic infection, toxins, and allergens. It may be that these associations that increase immunoreactivity connect the neuroendocrine system and the immune system to the origin of atherosclerosis. This is an example of that weblike thinking that is fundamental in functional medicine.

Upregulation of the immune system causes upregulation of the production of immune-inducible nitric

oxide synthesis. That upregulation increases oxidative potential by the production of peroxynitrite, causing all these other mutagenic injuries at the molecular level that may initiate atherosclerosis or atherogenesis.

Reactive Nitrogen and Oxygen Species in Atherosclerosis

Adipose tissue is a source of proinflammatory mediators. As a person becomes more obese, he or she produces more inflammatory mediators and, as an article in the *Journal of Lipid Research* recently pointed out, more nitric oxide. More nitric oxide synthase is produced in the adipose tissue from obese subjects, and more nitric oxide and inflammatory cytokines are likely to result. This process further complicates or contributes to the inflammatory linkage with atherogenesis. Insulin resistance and hyperinsulinemia metabolically encourage the deposition of fat as central adiposity, which subsequently alters the expression of these proinflammatory substances and upregulates their expression. That might be part of the connection between obesity and heart disease—through the inflammatory connection associated with adipose elaboration of these inflammatory mediators.

When you start producing a lot of nitric oxide, superoxide, and hydrogen peroxide, more peroxynitrite is also produced. Peroxynitrite is a very powerful nitrosating substance in tissue and plasma. It nitrosates proteins, which creates antigenically active protein that further activates the immune system and creates oxidative stress environments. In fact, they serve as cell-signaling agents in their own right, associated with the initiation of atherosclerosis.

The Complex Connection to Heart Disease Risk

An article in *Free Radical Biology & Medicine* indicates that reactive oxygen and nitrogen species, the combination of nitric oxide and superoxide, produce these reactive cell-signaling oxidants. Here is the oxidant connection to heart disease; linked through the inflammatory component of heart disease. It is related to the immune upregulation implicated in heart disease, which in turn is related to the neuroendocrine component through the role of insulin on adipose tissue formation.

Heart disease is the most significant risk factor for death in women after menopause. To reduce heart disease risk in a perimenopausal woman who is going into menopause, we need to look beyond her cholesterol levels. We need to look at her inflammatory state, her endocrine balance, and her neurological signaling system to best understand how to balance her function and extend her health span.

Nutritional Modulators of Inflammatory Cytokines

Some nutritional modulators can affect the production of inflammatory cytokines by the adipose tissue. One extensively studied nutritional modulator is green tea catechins. These substances in green tea, and in other teas as well, represent a complex array of interrelated flavonoid and other polyphenolic molecules that influence inflammatory mediation from adipose tissue and from other sites in the body including the gut, liver, and systemic white cells. In a recent animal trial, green tea catechins helped lower expression of inflammatory mediators and reduce body weight in animals who were genetically disposed toward obesity.

This paper appeared in *Endocrinology*. I emphasize that it was an animal trial, but epidemiological

studies and observations indicate that individuals who consume high amounts of green tea, two to three cups per day, have historically lowered body mass indices. That does not prove a causal association, but it is an interesting observation. To throw it into the mix again, there may be some interesting connection between obesity, inflammatory mediators, and insulin sensitivity.

Cell Growth Regulation

The regulation of cell growth is determined in part by the manner in which anabolic messages influence the cell signaling process, and includes insulin as a central signaling molecule in addition to its role in increasing the propensity toward oxidized LDL. Oxidized LDL, in turn, has a cell regulatory effect on mitogenic activity in cells, increasing cell proliferation. If you view an atheroma as a proliferative event, it represents a monoclonal hyperplasia (to borrow a term from Dr. Earl Benditt, author of an article that appeared in the 1978 issue of *Scientific American* titled, "The Origin of Atherosclerosis"). Dr. Benditt is a pathologist at the University of Washington School of Medicine. He has indicated that atheromas start off as single cell (monoclonal) hyperplasia, which undergo and are in effect like a benign tumor on the inside of the artery wall that might have been initiated by mitogenic agents, of which insulin and other signaling factors downstream from insulin.

Increases in glucose produce higher levels of glycation products; glycooxidation increases lipoxidation and LDL oxidation. Therefore, there is a close correlation between the toxicity of poorly managed glucose, or glucose dysregulation, and LDL oxidation.

With insulin resistance/hyperinsulinemia syndrome, there is an inability to transmit the message effectively from insulin to the glucose regulatory machinery, the cell signaling process that controls glucose transport and metabolism. You have increased risk of glycooxidation and glycation, as well as altered cell signaling and gene expression. Insulinemia emerges once again as a central factor across a wide range of neuroendocrine metabolic functions. An article in *Free Radical Biology & Medicine* discusses the relationship of glycooxidation and glucose toxicity to oxidation of LDL in atherogenesis.

The Role of Soy in Preventing Atherogenesis

Soy isoflavones and soy protein constituents play an important role in reducing the tendency of LDL to be oxidized and reducing the generation of oxidized LDL autoantibodies that may be associated with atherogenesis. Several studies on this subject have appeared in the last few months. One study on atherosclerosis-prone rabbits appeared in the *Journal of Nutrition*. Soy protein isolate was found to reduce the oxidizability of LDL and the generation of oxidized LDL antibodies when the rabbits were fed a high-fat, high-cholesterol diet.

Another paper showed the isoflavone components in soy are important as agents that modify the development of atherosclerosis and the oxidized and antibody effect in immune-regulated animals. Isoflavone aglycone-rich extracts without soy protein were found to attenuate the development of atherosclerosis in the same cholesterol- and high-fat-fed rabbits.

Complex Factors in Development and Prevention of Heart Disease

Many questions have been asked about soy recently. Is it toxic? If so, how toxic is it? I would summarize that discussion by saying "everything in moderation." We are not saying that if soy is good, a whole lot of soy ought to be better. We are saying soy is good in moderation—in the range of 50 to 70 mg per day of the isoflavone families from soy. That would represent one to three portions of soy products per day—soy milk, soy flour, soy meal, soy protein isolate. These are not toxicological doses.

We are beginning to recognize that diabetes is not just a cause of heart disease; that there are progenitor effects of insulin resistance/hyperinsulinemia. The drugs that modify insulin sensitivity will lower body fat, lower inflammatory mediators, and lower heart disease risk. These are drugs like the glitazones. We are witnessing a new recognition that diet can manipulate genetic expression in these cases to improve functionality. That sets the stage for our Clinician of the Month who will tell us how to moderate risk in women with neuroendocrine dysfunctions.

Interview Transcript

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Introduction: Background and Evolution in Endocrinology

JB: This month we are pleased to have as our Clinician of the Month Dr. Diana Lynn Schwarzbein, an endocrinologist from California. Dr. Schwarzbein attended the University of Southern California School of Medicine. She is board certified in both endocrinology and internal medicine and has been focusing her practice in Santa Barbara, California, in areas that are germane to the focus on functional endocrinology in this month's Functional Medicine Update. Dr. Schwarzbein is the author of a superb book, The Schwarzbein Principle, and companion books titled The Schwarzbein Principle Cookbook and The Schwarzbein Principle Vegetarian Cookbook.

Dr. Schwarzbein, it is a pleasure to have you as our FMU Clinician of the Month. Your career has taken you in an interesting direction in your practice. Would you tell us how you got where you are and where you're heading with your clinical practice at the Endocrinology Institute of Santa Barbara?

DS: After I graduated from USC medical school, I didn't even know if I wanted to be a surgeon or an internist. I thought that if I did internal medicine, at least I couldn't go wrong because I could always use that with whatever I did. After my three years of internal medicine, I got interested in endocrinology because I did a rotation in it.

At that time, I was doing a lot of work with hypo- or hyperthyroid patients and diabetics. I was very discouraged with treating diabetic patients, because I never saw anybody get better. I also was at USC

County Hospital and there wasn't any continuity of care there. When I finally left after the nine years of training at USC and came up to Santa Barbara, I was privileged to start a "diabetes clinic" here. The clinic where I had started working had been without the services of an endocrinologist for a few years, so I was asked to start it again. I thought that was the bread and butter of endocrinology, but I really wanted to get into other areas such as pituitary disorders and adrenal gland dysfunction, until I started working with the diabetics.

Working with Diabetic Patients

I got very excited because at first, when they were coming in, I kept hearing these stories about their being diabetic, and being diagnosed 10 years ago through routine blood work. When they got the results of the blood work, there was a red flag that indicated their blood sugar levels were slightly elevated. Their internist, endocrinologist, or physician asked them to go on the American Diabetes Association Diet (at that time it was a higher-carbohydrate, lower-fat diet). But as people came in, they were getting worse. Their blood sugars kept getting higher, they kept putting on more weight, their blood pressures were going up, and they had more coronary artery disease.

As I continued to see this influx of people, I kept saying something is wrong here. When I was seeing these diabetic patients, my work started switching over from adrenal gland and pituitary/thyroid disorders to hyperinsulinemia and insulin resistance. That's how I evolved to doing a lot of the work I'm doing today.

Evolving a Clinical Program to Treat Insulin Resistance/Hyperinsulinemia

JB: We have always been interested in this topic in FMU. Dr. Gerald Reaven was a COM within the last couple of years. A professor emeritus of medicine from Stanford, he coined the term "syndrome X." You have taken of the complicated endocrine associations with insulin resistance/hyperinsulinemia and translated them into a meaningful and applicable clinical program. Would you talk about the evolution of your program, how it has worked out, and how you've refined it over the years?

DS: It started with these diabetic patients. When they were coming in to see me, they would tell me I couldn't ask them to do the ADA Diet. They said they had been doing that and all they had evolved to were insulin injections. They would start on the diet, go to oral medications for diabetes, and finally to insulin. They said they were in my office because they were frustrated. I was very lucky to have a subset population come to see me when I first started my practice who were very motivated to incorporate whatever dietary and lifestyle changes were necessary in order to get better. It was very fortuitous.

I started to send people home to do blood sugar monitoring six or seven times a day before meals, right before meals, an hour after the start of each meal, and then at bedtime. I asked them to write everything down they were putting in their mouths, just to make sure they were following the ADA Diet correctly. When they would come back to see me, it was amazing, but it was also very obvious that what they were eating was wrong because their blood sugar levels were jumping more than 100 points from before to after a meal. You can only say that was an effect of the food they were putting into their bodies at that time.

Analyzing Patients’ Diets

The patients and I started analyzing what could be causing their blood sugar levels to rise so dramatically. At the beginning, I said I we needed to switch them to a very-low-carbohydrate, higher-fat, higher-protein diet, because I was extremely worried about coronary artery disease, as well as obesity in these patients. I started taking some of the carbohydrates away, because carbohydrates digest down into sugar. You're not going to turn amino acids into sugar in an hour, so it's got to be the carbohydrates that are making the blood sugar spike over the hour.

We started slowly removing some of the carbohydrates and adding more monounsaturated fats, trying to add a few more proteins. Initially, we started off with more vegetable proteins, because animal proteins have been associated with heart disease and kidney failure. This would have taken a long, long time if it weren't for what I call the "cheaters" in my program. These were patients who decided on their own that they were smart enough to do their blood sugars before and after, and whatever made their blood sugars stay down the lowest, that was what they decided they were going to eat more of. People started coming in having eaten more chicken, red meat, butter, heavy cream, and fish (although many people don't like fish that much). They were telling me they liked red meat better than fish and that it kept their blood sugar levels down.

Effects of Diet, Exercise, Caffeine

What I started seeing was weight coming down, blood pressure coming down, cholesterol levels lowering, and HDL levels rising. Even blood sugar levels coming down because that was the first target we were looking at. It was quite amazing! That was the beginning of the whole thing, and I was just looking at it from the standpoint of a food issue. Of course, we're always told to tell diabetic patients to exercise, but it wasn't really the main focus of the program; it was related to food and what you needed to do. After a while, we would get some nonresponders to the program as far as just the food was concerned. When we would add something like exercise, then their blood sugar levels would come down. Or we would tell them they were drinking too much coffee and caffeine raises adrenaline levels. Adrenaline is an anti-insulin hormone, so it's going to make you more insulin resistant. When we started tapering off caffeine, we would get a lowering of blood sugar levels in some patients whose blood sugar levels would not come down just by changing food alone.

It started with a one-step nutrition program and ended up being a five-tiered program, including stress management. Stress raises the stress hormones like cortisol and adrenaline, which are anti-insulin hormones. It was a healthy, balanced eating program. It was the tapering off of stimulants and increasing exercise. The last category has to do with hormone replacement therapy in the aging population. For women, it was estradiol replacement and for men, it was DHEA or testosterone, depending on which hormone was the lowest.

A New Type of Program: the Heart Disease Relationship

JB: It sounds as though the program is almost counter-intuitive relative to what some people have learned from Nathan Pritikin, Dean Ornish, or McDougal about the high complex carbohydrate, high-fiber, lower-fat, modest protein diet. Some people may feel this approach is atherogenic and likely to cause heart disease. Would you tell us about the approach you've been describing relative to heart disease risk?

DS: That was one of my first concerns. When we talk about risks for coronary artery disease, we say that

in the apple-shaped body with the weight around the upper middle, high insulin levels have been associated with coronary artery disease. Other factors are elevated triglyceride levels, high blood pressure, non-insulin-dependent diabetes, and diabetes in general, sedentary lifestyle, low levels of estradiol in women, and low levels of DHEA and testosterone in men. Look at a list of risk factors for heart disease and then look at the program. If you put somebody on a program that drops their blood pressure to normal without medications, normalizes their cholesterol levels without medications, gets rid of the visceral fat around the midline, replaces hormones that have been missing, and targets these known risk factors, it should decrease the risk of coronary artery disease.

But it goes deeper than that. Articles have been published throughout the last 40 years related to high insulin levels and the formation of atherosclerosis. They've shown that insulin is absolutely needed for plaque formation. Insulin is a growth factor for fibroblasts. Fibroblast proliferation has been shown to be a component of plaque. It is a growth factor for smooth muscle tissue, again be related to atherosclerotic plaque. It's thrombotic; in other words, it decreases fibrinolysis, so insulin has also been shown to increase clotting, and clotting is a major factor for atherosclerotic plaque.

Insulin Effects and a Program to Lower Insulin Levels

Insulin is one of the hormones that modulates cholesterol being dumped into the arterial smooth muscle cells. Now we know that the arterial smooth muscle cells are dynamic tissues. Also, their insulin will dump sugar or glucose into these cells and then turn on cholesterol production through the HMG CoA reductase enzyme. Insulin has been shown over and over again to play all of these roles that, at a cellular level, lead to the formation of plaque.

The earliest study was done in a dog. They infused insulin into one femoral artery and showed plaque formation in that artery and no plaque in the artery into which insulin was not infused. They were saying there was a local effect of insulin. Even as recently as 1996, the New England Journal of Medicine published an article about hyperinsulinemia as an independent risk factor for ischemic heart disease. They concluded that high fasting insulin concentrations appear to be an independent predictor of ischemic heart disease in men. My five-step program is designed to lower insulin levels.

Applying the Diet

JB: A companion paper that preceded the paper you mentioned was published in 1989 in the New England Journal of Medicine. It looked at risk factors for coronary artery disease in healthy people with hyperinsulinemia versus normal glucose tolerance and normal insulin. This study showed, again, increased risk in those with hyperinsulinemia and the so-called syndrome X individuals. Do you feel these individuals you're describing are a cohort or subset of the whole and that there are some people for whom a higher complex carbohydrate, modest protein, lower-fat diet would be preferable? Or do you believe this diet is applicable to all individuals with visceral adiposity and elevated cholesterol?

DS: That's a great question. It's actually going to be part of my next book, which I'm calling the Metabolic Continuum. The Metabolic Continuum to me is related to the way a person starts out to be insulin sensitive and becomes insulin resistant. That's how I look at this whole process. As you know, when we get older, we become insulin resistant just with age. I am looking at the process of insulin resistance not as a genetic issue, although there are people who are genetically insulin resistant, but more as an acquired

process. You have to know about some of the factors that raise insulin levels over time.

Do high insulin levels precede insulin resistance, or does insulin resistance precede high insulin levels? Right now there is a big controversy around that. I'm going to look at it from the viewpoint that we start off insulin sensitive and change with time. These are metabolic disorders, such as obesity, coronary artery disease, hypertension, and dyslipidemias, and we need to ask what are we doing to ourselves in order to change that.

The Carbohydrate Component

I start off by looking at a carbohydrate, which is nothing more than sugar molecules hooked up chemically. When you eat a carbohydrate, you need to digest it because it's too big a molecule to cross from the intestinal lining into the portal veins. It's going to be digested through digestive enzymes into single sugar molecules, which are small enough to be transported through the intestinal lining. They are transported inside (that's absorption), and when they enter the portal vein, they trigger the release of insulin. Insulin is released in proportion to how much sugar is entering the portal vein at a given moment. If I eat a higher carbohydrate diet, or just even carbohydrates basically mostly for that meal, I'm going to get a lot of sugar entering my portal vein at a given moment. That would raise the insulin levels higher for that given moment.

Processing Sugars in the Liver

You could carve up the glycemic index of the meal. The next place that food goes, because it has to follow a certain pathway, is directly into the liver. The liver is the great processor. It is made up of millions of cells surrounded by pools of blood that form sinusoids. This means that the surface area of the liver is very large. Insulin and sugar entering the liver together will be exposed to a lot of insulin binding sites or "doors." The binding of insulin to its "doors" causes the liver cells to take in the excess sugar coming from the circulation at a very efficient rate.

It does that because if the sugar didn't go into the liver cells and went out the other end to the bloodstream, you'd have very high blood sugar levels and you'd be a diabetic. This is a very protective pathway. The liver takes up most of the sugar after the initial meal. We start off with the liver cells being very insulin-sensitive. They will take up a lot of sugar and they will start processing the sugar. Sugar can be processed down into ATP and carbon dioxide and water, or it can be built back up again into the human carbohydrate called glycogen. But most of this excess sugar (I'm going to keep using that term because excess means for the given moment that it's entering) is not needed for energy right now. You might need it over the next 4, 6, 8, or 10 hours, but we're talking about what the body does with it at the moment it enters the system.

The Liver’s Role in Detoxifying Glucose

The liver has to process that excess sugar into triglycerides or cholesterol. Those are, if you will, the detoxifying pathways of glucose. Glucose is very oxidizing to the human system, and oxidation is much more damaging. It has got to be one of the major components, again, of coronary artery disease. Oxidation must occur to damage the cells to call upon the immune system to start all of these growth factors and clotting that are occurring at the level of the artery.

The liver, therefore, turns sugars into fats. Then it packages them in a protein coat. That is what becomes VLDL cholesterol. As we know, VLDL cholesterols leave the liver, travel through the bloodstream, and with the help of insulin and an enzyme called lipoprotein lipase, the triglycerides are removed from the VLDL to the different cells of the body. All the different cells of the body basically can use triglycerides or glucose interchangeably for energy, except for the brain cells, the red blood cells, and some of the kidney medullary cells.

Oxidizing Rate of Glucose and Fat

You're still going to get the food that you ate to your cells to be used as energy, because that's basically what glucose is used for anyway, but it's being detoxified into a fat because fats are less oxidizable. You can't oxidize fats at the high rate that you can oxidize glucose. If I turn my glucose molecule into a fat molecule, then I'm already protecting my protein cells and my protein cell components from higher oxidation. One of the biggest roles of insulin is to make sure that high levels of sugar don't leave the liver and go to the different cells of the body and damage them, because glucose is much more toxic than fats. I think we've been taught that fats are more toxic than glucose, or that glucose doesn't play a role in heart disease, but fats do. In reality, someone who has higher glucose levels and lower cholesterol levels is in the worst case scenario for coronary artery disease because of the oxidation of that glucose.

So the liver takes the sugar that enters, processes it, and uses some of it for energy. Some of it is stored as glycogen, but the main part of that glucose is going to be turned into fats and delivered to the cells. When all the triglycerides are off that VLDL molecule, it becomes an LDL cholesterol molecule. This is one of the ways we make LDLs in our body.
Stage I in the Metabolic Continuum

The LDLs will circulate to the cells, and again insulin plays a role in the receptor sites for cholesterol being dumped into the cells. The higher the insulin levels, the more cholesterol will get dumped into the cells. That is the first normal pathway. Now, back to the triglyceride pathway. If I'm young and I'm eating lots of carbs, my pancreas is responding and thinks it's great. My job is to put out insulin for the amount of sugar that I'm eating at a given moment, and it will do that. The liver can handle all the excess sugar and turn most of it into VLDLs. Then the cells think that's great, because they can use all of the triglyceride for energy right now.

I call that stage I in this metabolic continuum. In stage I, you have high insulin levels because of what you've chosen to eat. You're not aware of this because you can still stay thin. There's no physical sign that my insulin levels are high unless I ask what raises insulin levels. The answer is that a high-carbohydrate, lower-protein, low-fat diet would raise insulin levels. Then, as time goes on, as I'm getting older, if I continue to do the same thing (habits are born by what makes us feel good or what seems right) and if I'm not gaining weight, a lot of people think that they're doing the right thing. They continue eating the traditional American diet, which is higher in carbohydrates and, in the last 20 years, lower in fats.

Stage II

Then you start to lose a little bit of your lean body tissue. This occurs very slowly over time and is not noticeable. What happens next is that you don't need all that energy. It could be just because you're older now, and now you have a desk job versus when you were in school and had more physical activity, but

you don't change your eating habits. Slowly, I start not to need all those VLDL triglycerides for energy, so I will store them as fat cells. For men, because they have testosterone, the first place they will go will be around the midsection. For women with estrogen, you're going to see it more in the hips and thigh areas. Later on women begin to store fat around the midsection, and then you know your insulin levels have been high for a long time. You dump off the triglycerides to be used as energy, or in stage II, some of those triglycerides are stored away as fat.

What do most people do when they start to gain weight? They start to go on diets. Of course, if we look at it from a caloric viewpoint, fat has more calories than proteins or carbohydrates. A lot of people start thinking they've been eating too many fats and that they'd better cut those down. They start the whole cycle of less fats and more carbohydrates, fewer calories, so initially because of the fewer calories scenario, insulin levels will be lower. With time, because of fewer calories, they will trigger adrenaline, for instance, glucagon and cortisol. These are the hormones that will go looking for calories in your body. They will start breaking lean body tissue in order to be converted into glucose for the brain. Once glucose is converted into fats, the brain can’t use it as energy, because the brain needs glucose, unless I'm in starvation mode, and then I'm going to break my fats down into ketones to be used for energy.

Developing Insulin Resistance

If I'm just eating fewer calories throughout the day, I don't go into ketosis. Because I don't go into ketosis, I need to make new sugar to feed the brain, and new sugar is made through taking lean body tissue or proteins and converting them into glucose, or gluconeogenesis in the liver cells to feed the brain. When I do that, I start to lose my lean body tissue. Again, very small changes are occurring over time. What starts to happen is that I start setting up an environment where I'm going to start having more adrenaline, cortisol, and glucagon. These are the anti-insulin hormones that make me more insulin resistant. So I set up a hormone environment that also makes me more insulin resistant.

More time goes by. If I go back and forth, losing the weight and the insulin is going down, and then losing my lean body tissue and the adrenaline is going up, my insulin levels are going higher to overcome the adrenaline. I'm going to get myself more and more into this insulin resistant state. All of a sudden, I'm going to start having high triglyceride or VLDL levels because the triglyceride off the VLDL levels will not be able to get into the cells. It might be an intracellular reason; in other words, there might be a resistance in breaking down glucose in my cells. Or it may be hormonal. Adrenaline and cortisol block the action of insulin outside the cells, not letting the sugar or the triglycerides into the cells.

Stage III

I will back up that system, and I call that stage III. You start having high triglyceride levels and weight gain around the middle, and now you're insulin-resistant for the first time. In stage I, when you're able to use all that extra glucose for energy, you're insulin-sensitive. In stage II, even though you're gaining weight, you're still insulin-sensitive because you can still get all the triglycerides into the cell. In stage III, your are starting to become insulin resistant because your body is not able to clear in 12 hours all the food from the meal before. You develop high triglyceride levels. That will back up to the liver where, when I start eating carbohydrates and I digest them into glucose, insulin won't be able to get that glucose into the liver cells. The glucose will go through the liver to the main blood system. Now I have high blood sugars and I'm a type II diabetic.

That is the way I view the process of going from insulin sensitivity to insulin resistance, just from the viewpoint of eating incorrectly. But it takes more than that. Usually, I need to have other things that raise my enzymes and hormones. Examples could be stress, skipping meals, drinking lots of caffeinated products, smoking cigarettes with nicotine in them, or being on birth control pills. Birth control pills give women too much androgens and not enough estrogen and make them more insulin resistant. It's a continuum of what I have to add of all these things that are going on in my life over time, and how did I start off with this wonderful body that works and is doing everything it needs to do, and then end up insulin resistant?

Central Adiposity and Hyperinsulinemia: Which Came First?

JB: That was a great overview of intermediary metabolism. Is the obesity we observe—the central adiposity, visceral adipose tissue deposition, apple body shape, increased waist-to-hip ratio—caused by the insulin and hyperinsulinemia/insulin resistance, or does the obesity produce insulin resistance?

DS: I believe it can be both ways, but I think the rise in insulin resistance is more in the high insulin levels causing insulin resistance. But you can certainly look at it from an intracellular defect viewpoint. What's going on intracellularly? Do I metabolize glucose as efficiently as somebody else? If the glucose intermediary metabolites are in the cells, then you start turning out the enzymes that break glucose down into ATP. I think you can have genetic defects and I think you could ask why members of one family get diabetes from the same set of poor insulin lifestyle habits and another family does not. There's probably something else going on in the cell at the same time.

For the first time we're seeing teenagers becoming insulin resistant. We've never seen type II diabetes in this many teenagers in the history of medicine. I think there is definitely an acquired form that's playing a bigger role today. It has to do with the fact that kids have been brought into a world in which we're saying high carbs and fats are bad for you. All the textbooks are saying to stay away from fats, and the kids do really buy into that and stay away from the fats. But then we're not feeding them real food, so they're eating a lot of junk food or pasta and they're drinking a lot of carbonated beverages with caffeine in them. Or, they're skipping meals and setting up this environment in which their insulin levels keep getting higher and higher. We're now seeing what I call this metabolic continuum, which used to happen over 40 or 50 years, happening over 20 years. I believe there are two components to it. There will always be a genetic component to everything, but I think we have more control over our hormones than we've been led to believe.

Insulin Resistance and Central Adiposity

JB: Is insulin resistance/hyperinsulinemia the precipitating factor in the development of central adiposity? According to traditional dietetics, weight gain is a problem with the first law of thermodynamics. Energy in has to be balanced with expenditure of energy out, which makes good sense if you believe in the conservation of energy, which most of us do. However, many other factors contribute to the way those potential energy calories are processed, which is controlled in part by this symphony of hormones you described. Do the hormones regulate the processing of calories, which then leads to deposition of fat for a rainy day that never comes?

DS: My viewpoint on that, since I work with diabetics and I feed them a lot of calories and they lose

weight anyway, is that this is not a matter of calories in/calories out. For me, metabolism and energy expenditure are under hormonal control. Insulin is a hormone that tells us to store food for later. Adrenaline is a hormone that tells us to break it down and use it now. Cortisol says break down the proteins, but store the fats. Growth hormone says make proteins and get rid of the fats. So I look at it from the standpoint of balancing out these major hormones for metabolism.

If you're eating the right foods and doing the right things that trigger these different hormones, you will not gain weight no matter how many calories you're eating. The only reason I believe this is because of the work I've been doing in the last 10 years. I was certainly taught that calories in equal calories out, but I have found that the more a patient doesn't eat, the higher the insulin levels will go with the next meal. You can create hyperinsulinemia, for instance, by skipping breakfast. If you skip breakfast, you are going to have high adrenaline because your brain still asks, where's the glucose? So your body will use the adrenaline to help break down some lean body tissue, and that activates the enzymes in the liver for gluconeogenesis, and you feed your brain that way.

Low-Calorie Eating and Weight Gain

By the way, when you are doing that, your appetite is suppressed. But then, lunchtime comes around and this will be the first meal of the day. When you eat, because adrenaline has been high all morning, it exerts its effect as an anti-insulin hormone. It's already telling the body the next time food is there to put out more insulin. So you become hyperinsulinemic because adrenaline has been high. For the same amount of carbohydrates that might have caused you to secrete a smaller amount of insulin, you're now going to secrete a higher amount of insulin because you have to overcome the higher adrenaline levels in your system at the given moment. That is what starts creating hyperinsulinemia. I have found that patients who do things that raise adrenaline and raise insulin—low caloric eating, which raises adrenaline and triggers higher insulin levels—are the patients who gain the most weight. That's been my experience.

Insulin and Sex Steroid Hormones

JB: I think, based on your continuum of metabolic types with insulin, you would probably agree that polycystic ovary syndrome is the endpoint of a series of events of increasing androgenicity in women. Would you comment on the insulin connection to the sex steroid hormones?

DS: Stress doesn't raise insulin directly; it raises it indirectly, through adrenaline and cortisol. Skipping meals raises it again indirectly through adrenaline and stress hormones. Eating too many carbohydrates raises insulin directly. Stimulants raise it indirectly. Exercise lowers insulin levels. What we've seen is that you end up with a high-insulin lifestyle. Insulin is a hormone that increases androgen production. So you'll have increased androgen production. For women, in the first half of the cycle during the follicular phase when the egg in the follicle is growing, estradiol levels need to rebind to the cell surface to cause that egg to grow further. Androgens will block the binding of estrogens.

It seems as though the high androgen environment is not letting that egg fully mature. If that egg doesn't fully mature, and you don't get a peak estradiol level, and then it doesn't drop precipitously, you don't get an LH surge. We're seeing anovulatory cycles. We're ending up with lower estradiol levels, but higher in relationship to progesterone, and then, no progesterone from anovulation. That is setting up the anovulatory cycle. Now, if I have lower estradiol levels, that feeds back to becoming more insulin

resistant, because estrogens have been shown to cause insulin sensitivity. I think that's where the feedback loop comes in.

Insulin and Sex Hormones

I think it's high insulin causing high androgens causing lower estrogens causing no ovulation, and then the low estrogens coming back and causing more hyperinsulinemia. Now you've got a cycle that will continue. I have used my five-step program of stress management, healthy eating, tapering off chemicals, exercise, and hormone replacement therapy, if necessary. Again, with Stein-Levanthal patients, I don't always do that. In lowering insulin levels and reversing this process—this was before the advent of physicians using medications like Metformin to do the same thing, or Glucophage, which sensitizes you to insulin, I've seen that happen. I've used the same program in Stein- Leventhal patients and we've completely reversed the process.

Evaluate Insulin Sensitivity before Prescribing HRT

JB: I hope the listeners recognize, based on what you have so eloquently reported, that to move quickly into hormone replacement therapy (HRT) in women who may have estrogen/androgen imbalances, without first evaluating insulin sensitivity, might be ill-advised. They ought to look at precipitating or antecedent factors before they get into the HRT model.

DS: Yes. I would like to make a plea here. Don’t use birth control pills, because you'll get a menstrual cycle, but you'll create more hyperinsulinemia because birth control pills are more androgenic They're more like testosterone than progesterone. It has been shown that high testosterone feeds back to high insulin; it’s like saying low estradiol feeds back to high insulin. You can create the environment of still having high insulin levels even if you're giving a higher estrogen birth control pill without fixing the initial physiology. We should go to the cause and try to reverse the physiology if that's possible.

The Schwarzbein Principle

JB: Thank you, Dr. Schwarzbein, for this extraordinary discussion. I want to remind our listeners that The Schwarzbein Principle is a reader-friendly book for patients. They can take away both this information and the diet approach you described in the book. You have the corresponding cookbooks with your book to assist in application of the program. You've done a tremendous job in helping us understand this complex topic. On behalf of all our listeners, thank you for assisting us in our education.

DS: Thank you so much for letting me tell you how I think it works.

Insulin Resistance and Atherosclerotic Cardiovascular Disease, Upper Body Adiposity, Obesity, Hypertension, and Dyslipidemia

Taking a complex topic like endocrinology, distilling it down, and verbally communicating it in such an understandable way is a tremendous skill. I think Dr. Schwarzbein has been "a good teacher" in her presentation.

We have been discussing the insulin resistant/hyperinsulinemia complex for several years now

on *FMU,* and this is another important chapter in the evolution of this topic. The connection between insulin and atheroma is significant. In fact, 20-year prospective follow-up trials or studies have looked at the relationship. One such study was published in *Diabetes Care* in 1990. This paper does a meta-analysis of the relationship between insulin response to an oral glucose load, and the relationship, ultimately, to atherosclerosis or atheroma. As Dr. Schwarzbein pointed out, and as Dr. Reaven brought to our attention, it is clear that the hyperinsulinemia/insulin resistance syndrome is a major cholesterol-independent risk factor to cardiovascular disease.

Hyperinsulinemia and Ischemic Heart Disease

These broad-based studies support the independent association between hyperinsulinemia and ischemic heart disease. Hyperinsulinemia is associated not only with raised triglyceride levels, but also with decreased HDL. A clinical hallmark is an elevated fasting triglyceride-to-HDL ratio in the plasma, generally about 5:1. That generally means reduced HDL and elevated triglyceride. We also talked about upper body adiposity with increased waist-to-hip ratio. Generally, the ratio is .8 or greater. With anything above .8 with increased body mass index, we also start thinking about hyperinsulinemia and insulin resistance syndrome.

There are dense LDL particles associated with hyperinsulinemia. Even with normal cholesterol, you might have more of the dense atherogenic LDL particles. That may also be associated with increased LDL oxidizability and increased free radical oxidant stress, which has to do with atherogenic risk, as well. In this discussion in *Diabetes Care,* Dr. Robert Stout discusses the 20-year perspective on this group of studies that have all indicated is a stimulator to atherosclerosis.

Impact of Insulin Resistance/Hyperinsulinemia Syndrome

This insulin resistance/hyperinsulinemia syndrome has a tremendous relationship that extends beyond non-insulin dependent diabetes mellitus. Only a small percentage of people with insulin resistance may ultimately be diagnosed with type II diabetes. The greatest impact is seen in obesity, hypertension, dyslipidemia, and atherosclerotic cardiovascular disease risk. I am referring now to another paper in *Diabetes Care*. This broad-based review of many studies indicates strongly the insulin resistance connection to heart disease and other markers of dysfunction.

Dr. Schwarzbein mentioned the glycemic index connection. I think it is important to recognize that it may be any dietary and lifestyle variable that decreased the tides of insulin that are really important. We talk about the importance of high protein, higher fat, and lower carbohydrate, but the real question is, what kind of carbohydrate, what kind of fat, what kind of protein, what kind of fiber? What is the matrix of the diet? What is the physical nature of the diet? Is it highly processed or in an unrefined state? All of these questions have to do with very important factors leading to the kinetics of digestion and release of glucose across the lumen and the effect that it has kinetically on insulin regulation and the other hormones we have described.

Consider the Rhythms of Physiology

We should be careful not to jump too quickly to the conclusion that fats are good and carbohydrates are bad. Instead we should talk about the matrix effect that influences insulin-release mechanisms, the

kinetics of insulin release. Dr. Schwarzbein helped us understand this process. Dr. Sidney Baker also talks about this in his book, *The Circadian Connection*, explaining the important role of the rhythms of physiology in determining these outcomes.

The matrix of the diet, the nature of carbohydrate, the amount and type of fiber, and how quickly sugar is delivered to the cells are all variables the clinician can use in constructing the right diet for a patient. *The Schwarzbein Principle* in the diet approach is a useful way to start down this road.

That concludes this month's *FMU*. We hope you will be with us in March.

Bibliography

1. Weinstein JN. Pharmacogenomics--teaching old drugs new tricks. *N Engl J Med.*2000;343(19):1408-1411.
2. Esteller M, Garcia-Foncillas J, Andion E, et al. Inactivation of the DNA-repair gene MGMT and the clinical response of gliomas to alkylating agents. *N Engl J Med.*2000;343(19):1350-1354.
3. Gross CG. Neurogenesis in the adult brain: death of a dogma. *Nature Rev/Neurosci.*2000;1:67-73.
4. Lindahl B, Toss H, Siegbahn A, Venge P. Markers of myocardial damage and inflammation in relation to long-term mortality in unstable coronary artery disease. *N Engl J Med.* 2000;343:1139-1147.
5. Packard CJ, O'Reilly DS, Caslake MJ, et al. Lipoprotein-associated phospholipase A_2as an independent predictor of coronary heart disease. *N Engl J Med.* 2000:343:1148-1155.
6. Rader DJ. Inflammatory markers of coronary risk. *N Engl J Med.* 2000;343:1179-1182.
7. Elam MB, Hunninghake DB, Davis KB, et al. Effect of niacin on lipid and lipoprotein levels and glycemic control in patients with diabetes and peripheral arterial disease.*JAMA.* 2000;284(10):1263-1270.
8. Liu S, Manson JE, Stampfer MJ, et al. Whole grain consumption and risk of ischemic stroke in women. *JAMA.* 2000;284(12):1534-1540.
9. Podrez EA, Abu-Soud HM, Hazen SL. Myeloperoxidase-generated oxidants and atherosclerosis. *Free Rad Biol Med.* 2000;28(12):1717-1725.
10. Elizalde M, Ryden M, van Harmelen V, et al. Expression of nitric oxide synthases in subcutaneous adipose tissue of nonobese and obese humans. *J Lipid Res.*2000;41:1244-1251.
11. Patel RP, Moellering D, Murphy-Ullrich J, Jo H, Beckman JS, Darley-Usmar VM. Cell signaling by reactive nitrogen and oxygen species in atherosclerosis. *Free Rad Biol Med.* 2000;28(12):1780-1794.
12. Kao Y, Hiipakka RA, Liao S. Modulation of endocrine systems and food intake by green tea epigallocatechin gallate. *Endocrinol.* 2000;141(3):980-987.
13. Chisolm GM, Chai YC. Regulation of cell growth by oxidized LDL. *Free Rad Biol Med.*2000;28(12):1697-1707.
14. Benditt EP. The origin of atherosclerosis. *Scientific American.* 1978;201:74-86.
15. Baynes JW, Thoppe SR. Glycooxidation and lipoxidation in atherogenesis. *Free Rad Biol Med.* 2000;28(12):1708-1716.
16. Damasceno NR, Goto H, Rodrigues FM, et al. Soy protein isolate reduces the oxidizability of LDL and the generation of oxidized LDL autoantibodies in rabbits with diet-induced

atherosclerosis. *J Nutr.* 2000;130:2641-2647.
17. Yamakoshi J, Piskula MK, Izumi T, et al. Isoflavone aglycone-rich extract without soy protein attenuates atherosclerosis development in cholesterol-fed rabbits. *J Nutr.*2000;130:1887-1893.
18. Akazawa S, Sun F, Ito M, et al. Efficacy of troglitazone on body fat distribution in type 2 diabetes. *Diabetes Care.* 2000;23(8):1067-1-71.
19. Despres JP, Lamarche B, Mauriege P, et al. Hyperinsulinemia as an independent risk factor for ischemic heart disease. *N Engl J Med.* 1996;334(15):952-957.
20. Zavaroni I, Bonora E, Pagliara M, et al. Risk factors for coronary artery disease in healthy persons with hyperinsulinemia and normal glucose tolerance. *N Engl J Med.*1989;320:702-706.
21. Stout RW. Insulin and atheroma. 20-yr perspective. *Diabetes Care.* 1990;13(6): 631-654.
22. Defranza RA, Ferrannini E. Insulin resistance. A multifaceted syndrome responsible for NIDDM, obesity, hypertension, dyslipidemia, and atherosclerotic cardiovascular disease. *Diabetes Care.* 1991;14:173-194.

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