

January 2010 Issue | Suzanne Craft, PhD Professor University of Washington

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Welcome to *Functional Medicine Update* for January 2010. I always love starting a new year. To me, a new year is so refreshing and exciting. We're not exactly sure what the year will bring, but we know how much can change. You can see how dramatically and rapidly the field of functional medicine is changing already: epigenetics, hormesis, gene expression, intercellular signal transduction and the connection between the outside environment and inside cellular function. All of these things can affect function of cells, organs, tissues, organ systems, and whole-body signs and symptoms. In terms of chronic, age-related, progressive disease, new research may lead to new mechanisms of both prevention and treatment. I think the term "functional medicine" will come to be seen as fairly prescient. A lot of the dysfunctions that we later call pathology start early on as dysfunctions in functional physiology (in the network of interconnectedness within the cellular milieu). Organelles are influenced and molecular signals affect gene expression and epigenetics. It is a very rich and robust time of a changing paradigm in health care.

Ultimately the objective is not just to intellectually titillate us, but to really deliver more effective and safer interventions and therapies for individuals with progressive age-related diseases. It is to achieve what we have been talking about for many years, which is the concept that James Fries brought us to recognize in 1980. That is to compress morbidity, rectangularize the survival curve, and allow people to live to the limits of their biological age determinant and have a natural death (to pass on to the next level without significant years of infirmity). That is the objective, that is what a healthcare system is all about, and that is the reason functional medicine came into being: to put health into the equation of the disease-care system.

Let me start 2010 by talking about another major change that is occurring within health care: the nature of pharmacotherapy. Pharmacology, over the last hundred years, has been what we call "a-pill-for-an-ill"-type concept. A single molecule (generally) is used to treat a single endpoint to produce a single disease treatment. With this model, we have statins for cholesterol, or we have SSRIs for depression, or we've got H2 blockers for hyperacidity and gastric reflux, or we've got ACE inhibitors for blood pressure, etc. This model has been fairly successful in building a very profitable and robust pharmaceutical industry, and has led to many, many tools within the *Physician's Desk Reference* that are very valuable in managing crisis (managing acute illness by blocking, inhibiting, or having some antagonistic effect upon one metabolic step within this complex tree that we call intermediary metabolism).

If we think of a selective serotonin reuptake inhibitor (and, similarly, HMG co-A-reductase inhibitors), it has a specific effect on an enzyme that regulates serotonin dynamics. If we assume that the effect of statins is to block that enzyme (that rate limiting step in cholesterol biosynthesis), we're led to believe that

we can block that enzyme and inhibit the production of cholesterol from the mevalonate pathway, and thereby reduce the risk and incidence of coronary heart disease. These are all "single-hit"-type of mentalities: find a very high potency and a low-IC₅₀ (meaning the dosage required to inhibit something being very low), and that becomes a molecule of choice that is taken from phase 1 through phase 3 of the FDA investigation and approval process, and ultimately results in an approved medication for a clinical condition.

This model, as I said, has been successful. It was born out of the development of a pharmacology around antibiotics early in the 20th century. Antibiotics-fungal metabolites like penicillin-are really remarkable discoveries that birthed an industry that was buoyed with enthusiasm and confidence around this pill-for-an-ill/single-hit-type of approach. Antibiotics are specifically focused on blocking a series of specific metabolic steps that are unique to bacteria, primarily those necessary for construction of their cell walls. By blocking the production of the cell wall, the bacteria are able to be a viable bacterium and this is called an antibiotic.

What is unique about this chemotherapy is that humans don't have the type of cell walls in their eukaryotic cells, and we generally call these cell membranes. For example, humans don't have the polymer of n-acetylglucosamine and n-acetylmuramic acid, which is part of the constituency of bacterial cell walls. As a consequence, the selectivity of the antibiotic is very high for the diseases associated with certain bacterial infections, without having an effect upon the physiology of the host cell (the eukaryotic mammalian cell). It's a wonderful pharmacological concept/paradigm that sounds so specific and so marvelous that we built a whole edifice around this that is presently our medical school education.

Some Agents are Extraordinarily Useful in the Short-Term, but Long-Term Use is a Concern

To a great extent, this paradigm has worked. By blocking or inhibiting certain steps in this complex web of metabolism, we are able to take charge of metabolism in a very specific way. There is no ambiguity in the emergency room when you give these drugs. They allow for the lockdown or the control of specific processes that may be deranged. The difficulty is encountered when we try extending this model to chronic illnesses, where you are blocking a specific function very efficiently over many, many years of pharmacology with a patient. The particular effect that was seen as benefit in the acute stage may have an adverse effect in the long term because in other cells you are blocking some of the fundamental positive effects that are necessary to regulate proper function.

As an example of this, let's discuss the use of things like TNF-alpha blocking agents (monoclonal antibodies) that have been developed in the generation of these new, disease-modifying anti-rheumatic agents (or DMARD drugs) that are used in rheumatology. These are extraordinarily useful in the short-term for blocking the acute pain of inflammation in arthritis. But over the long-term, the black box warning on these drugs suggests things like "Be cautious of opportunistic infections," or maybe "Be cautious of increasing risk to lymphoma." The reason for that is, over the long-term, by blocking TNF-alpha, which is in excess and enhancing the inflammatory response and causing joint injury and musculoskeletal injury, the drug is also blocking some of the favorable effects that TNF-alpha has in immune defense. So the price to be paid over the long term could be increased risk to opportunistic infection or lowered surveillance of transformed cells and malignancy.

These are the kinds of things that occur when you extend an acute rescue remedy (a pill-for-an-ill drug) into a chronic disease management approach. It may be that worrisome adverse drug reactions can start

appearing. The classic example people often use is Vioxx. Vioxx was a wonderful, successful, high-affinity, selective COX-2-inhibiting drug that was useful for management of acute inflammatory pain. Then people began to extend use over long periods of time for chronic pain. Now this very efficient drug-highly potent-was blocking COX-2 not only where it should (in the inflamed areas of the body), but it was also blocking it in the vascular endothelium and preventing proper prostacyclin formation, which is necessary to prevent platelets from adhering and forming thrombi. Now you start to get increased thromboses and risk to stroke and heart attack in genetically susceptible individuals.

These are the kinds of conditions that occur when you have very strong molecules that are very effective in the acute management of a condition that are extended into a longer term management program. What's the alternative to that? I think that's an interesting question. What's the good news? The good news is there is an emerging paradigm of pharmacology called network pharmacology, which may be the next major paradigm in drug discovery and development. I think this next paradigm is reflective of what probably has gone on naturally in our environment, relative to how natural substances in our food and things that we consume have been influencing our physiology through time in memoriam.

What is Network Pharmacology?

What is network pharmacology? Rather than trying to develop one single molecule that has a very high affinity for a substrate, where ligand-substrate interaction then blocks the function of a particular metabolic activity through inhibition, network pharmacology is defined as a molecule that has pleiotropic effects that modulates multiple steps along the metabolic pathway associated with disturbed metabolism and diseases of that outcome, and does so in a more mild way. Rather than blocking one thing in a very tough way-a very rigid, high-affinity way-a network pharmacological approach would have the ability to influence many things that cluster together to regulate the function that is associated with that pathology, but in a more mild way each step along the road. It still allows what is called "housekeeping" function in cells or tissues or organs that you want to be maintained. By maintaining housekeeping function, you maintain the good functions of those processes. By blocking (through this network pharmacology) the high points of activated function, you attenuate that, modulate those effects, and do it in a safer way because you're allowing the housekeeping function to be resident and still active where it is needed.

I hope you understand what I just said. This is a very interesting contradiction or contrast to the way we have traditionally thought about pharmacology, which is single agent to single outcome, and finding the highest potency drug with the highest affinity for inhibiting that substrate. What we are doing in this particular model is looking for things that may have a little less activity for a substrate, but much more regulatory effect over a series of steps in that network that are distorted and associated with that specific pathology. We are still modulating the function, but not inhibiting a specific step in that function to where we start getting adverse drug reactions occurring elsewhere. It's a very interesting concept, and has been eloquently described in a recent review article that appeared in *Nature Chemical Biology* under the title "Network Pharmacology: The Next Paradigm in Drug Discovery."¹ In this article the authors write about this dominant paradigm I've talked about in drug discovery: the concept of designing maximally selective ligands to act as individual drug targets to inhibit those steps in metabolism.

Many effective drugs act via modulation of multiple proteins rather than single targets. Advances in systems biology (which is a theme that underlies that of functional medicine) are starting to reveal that there is a robustness in this network structure of metabolism strongly suggesting that exquisitely selective compounds (very strong drugs for single activities), compared with multi-target, more mild drugs, may

exhibit not-so-good effects or undesired long-term clinical safety issues over years of use in a patient. This new appreciation of the role of poly-pharmacology and network pharmacology has significant implications for tackling the major issues of chronic disease management, including both safety and efficacy. We have talked about improved safety, but also efficacy may be improved by allowing attenuation of multiple steps within a group of a distorted family of metabolic steps that then regulate, overall, signs and symptoms at the whole-organism level more effectively than single-agent pharmacology.

The Significance of the Kinase Pathways

This is a very interesting new approach that I think is being developed. I find it very interesting because it is very similar to the way that nutrients and phytochemicals have recently been discovered to influence cell signaling and gene expression through the kinase signaling pathways. They do so by multiple hits in families of inter-related kinases, rather than just very hard hits of a single step in metabolism.

That makes pretty good sense, doesn't it, when you think of it from a teleological argument? Why would the things we eat in our foods have robust effects on multiple pathways in a milder way than single hits? Think of what would happen if we had agents in our foods that had the same pharmacology as our drugs. Every time we ate, our physiology would whipsaw all over the map and we'd be kind of a mess. Rather, we have evolved a relationship with the bioactive ingredients in our diet so that these molecules modulate function across network pharmacology to enhance or influence function in cell signaling and ultimately gene expression and epigenetics (and the phenotype of cells, tissue, organs, and organ systems over time) in a very mild way—a way that modulates their function versus therapeutically blocks function.

Vitamin D as an Example of Pleiotropic Influence

In 2008, *Alternative Therapies* published a guest editorial that I wrote titled "The Future of Nutritional Pharmacology."² I tried to address how we are seeing an emergence of a new understanding of nutrients, even in things like vitamin D. The vitamin D receptor signals through multiple different pathways to regulate function across a wide range of cellular physiological outcomes (not just a single hit). We often think of vitamin D as the "bone vitamin," but now we recognize it is really a pro-hormone and it has intercellular signaling effects. It interacts with the vitamin D receptor in a very significant number of pleiotropic ways to influence function across so many different organs and that is why we now see so many signs and symptoms related to vitamin D insufficiency. Vitamin D may be a useful substance for modulating so many different disease-related entities.

I think it is a different model. We are now starting to recognize this model probably has more historic implications relative to the way our physiology has been modulated over time than the pharmacology that has been developed over the last 150 years. This construct (that there are substances within our food and in our environment that can influence multiple signaling pathways and influence what we call network pharmacology) then suggests that these kinases—these some 500 different enzymes that are expressed in cells that transduce messages from outside the cell to inside the various organelles in the cell to alter cellular function—must be also modulated in a network way through natural substances, including nutrients that we find in our food (macronutrients, micronutrients, vitamins, and phytochemicals). That's what is starting to emerge to be much more well-understood.

Published articles have appeared just within the last few years on the role that various nutrients have in influencing these kinase signaling pathways through a network effect (not just a single kinase, but

through families of inter-related kinases that regulate cellular function). New therapeutic agents are being developed to modulate these kinase pathways in kind of a network-sympathetic, peaceful way, turning promiscuous, heavy-hitting, kinase-inhibiting drugs that have been used in cancer therapy, for instance, into new types of therapeutic agents that are safer and that have modulating effects across networks of kinases that then regulate distortion of the net of physiology (the system of physiology). In fact, this has actually been discussed very beautifully in a recent review paper about turning the promiscuous kinase-inhibitor drugs into safer drugs by influencing positively their ability to modulate, in a more mild way, individual kinases, but across multiple kinases as polypharmacology. This article appeared in *Trends in Biotechnology*, and this whole construct of modulation of kinases to produce safer chronic disease management therapeutics was discussed.³

I think we are starting to see an extraordinarily interesting pharmacology develop out of these new discoveries. I was very intrigued when I saw an article in *Nature Biotechnology* titled "New Therapies from Old Medicines," which is about botanical drugs-how they actually work and their potential future in developing new therapies for management of chronic disease.⁴ In this article, the authors write about the fact that there are multiple molecules within a botanical (it's not a single molecule), and each individual molecule in the mixture that is extracted from those botanicals may be a weak agent relative to its ligand binding. These botanicals would normally not pass muster with a pharmacologist who might say, "Well that's really too weak and has too high an IC₅₀ to really be an effective drug." But when you put them together in a family of interrelated molecules and see how they work in cellular systems, you find that they may be modulating a network of interrelated functions. Each one of the effects could be fairly minimal (or let's say lower activity), but taken as a family of interrelated activities, they modulate the distorted web to produce improved function.

In phytomedicines and phytopharmacology, this is often referred to as an adaptogenic effect. This means we are helping the cell find the right adaptation to its environment and modulate function rather than just produce inhibition of a specific function. This adaptogenic quality occurs when you have therapeutic agents that have more mild activities for ligand binding and can serve, really, as almost agonist/antagonist. They have effects of both loss-of-function and gain-in-function capabilities as it relates to their activity at the active site of various target molecules. These safer drugs might actually start emerging from the pharmacology of phytomedicines and from that of nutrients that have been found in our foods, particularly colored, complex, phytonutrient-rich foods.

Resveratrol is Another Molecule with Pleiotropic Influence

That concept can even be taken into the recent discussion around resveratrol, which has gotten a lot of press recently. Resveratrol is a stilbene-like molecule. It has a phenolic structure. It has a capability to modulate the SIRT1 genes (the histone deacetylases) that are involved with epigenetic alteration of genomic message expression. These SIRT genes have to do with regulation of insulin and inflammation and what has often been called longevity-related functions.

Resveratrol is a molecule found in foods about which we would say, "Well it has a specific action." But with further discoveries, it has now been found to have pleiotropic effects on multiple pathways that are interrelated to distortions of physiology that we often associate with chronic disease, like hyperlipidemia, insulin-related hyperinsulinemia/insulin resistance and diabetes. There are things within foods-molecules or families of molecules-that influence cellular physiology in a different way than that of a high activity/single molecule inhibiting a single step in a physiological network to produce a single outcome

(so that's that "pill for the ill"-type mentality). These more mild molecules are regulatory molecules that have effects over longer periods of time. That construct may be very desirable and is starting to gain traction. It is starting to gain a placeholder in the mindset of pharmacology, therapeutics, and ultimately the development of a science-based new medicine

Let's talk about one of the most significant concerns people have about altered physiology over the course of their life, and that's cognitive function, or Alzheimer's disease, or dementia. There has been a search (a very extensive search since the decade of the brain) to try to understand neuropathologies and try to get a better mechanistic understanding of neurodegenerative diseases. Certainly tremendous strides have been made, as have been chronicled in an understanding some of the molecular pathologies associated with neurocognitive disorders, like Alzheimer's disease, and Parkinson's disease.

What we are starting to recognize is that the principal mechanism by which these conditions occur over years of living is through interaction of genes with environment to induce altered cellular signaling, which then creates an environment in that region of the body (say the hippocampal region of the brain in Alzheimer's disease) that induces things like neurofibrillary tangles, tau protein release, the amyloid bodies that we associate with amyloid protein deposition, and ultimately apoptosis of that neuron that leads to cell death and lowered neuronal function and neuronal reserve.

Mechanisms are starting to be understood. We know about the relationship to inflammation. And we know about the relationship to oxidative stress. And, as has been discussed extensively in FMU in the past, we know about precipitating triggers that might induce some of this, things like alpha gliadin in people who are gluten sensitive. We just spent, in the summer of 2009, two issues of *Functional Medicine Update* going over, extensively, the role that these specific molecules in grain-related products can have--deleterious effects as neurotoxins in some individuals through activation of the immune system, and production of antibodies against various neuronal tissues, and triggering some of these processes as it relates to oxidative injury, apoptosis, and neurofibrillary tangle production.

Studies on the Mediterranean Diet and Cognitive Impairment

It is starting to be recognized that some of the triggers for neurocognitive degenerative diseases occur through environmental/gene interaction. As a consequence of that, studies have been published looking at dietary relationships to both Alzheimer's disease and Parkinson's disease. It is really quite fascinating to see these data accumulate.

A paper that I think reflects this emerging understanding appeared in *Annals of Neurology* and titled "Mediterranean Diet and Risk for Alzheimer's Disease."⁵ The investigators did a case-controlled evaluation over time looking at the appearance of Alzheimer's disease in individuals who self-subscribed to consuming a Mediterranean-type diet versus those who were on kind of an ad-lib diet (more of what we might call a traditional Westernized, more highly processed, higher sugar/higher saturated fat diet). They did incidence-of-Alzheimer's-types of evaluation over years (actually they followed these individuals for ten years), and they found a highly statistically significant difference between the rate of appearance of Alzheimer's dementia in those that consumed the ad lib diet versus self-subscribed to the Mediterranean diet. Again, these are association studies, they are not intervention trials-I want to be very cautious that we don't overstate the point-but the associations are quite strong between the compliance and adherence to a Mediterranean diet and the relative reduction in incidence over time (over a ten-year period of time) of Alzheimer's disease.

You might ask the question: Does this follow also for mild cognitive impairment? I'm talking about memory loss, in which a person doesn't have Alzheimer's, but they say, "As I'm getting older I seem to be losing my short-term memory and I just can't pull things back as well as I used to be able to." There is another similar study that was published that addresses this. It was also published in the *Archives of Neurology* -in 2009-in which the investigators looked at the relationship between those who consumed a Mediterranean diet and mild cognitive impairment.⁶ This is kind of your functional stages (pre-Alzheimer's); we're not talking about going all the way to pathology. They used standard psychometric questionnaires to evaluate cognitive function in these patients. The setting for this study was New York City, and people self-selected to be on a Mediterranean diet versus those who were on the standard American diet. What they again showed is that the higher the compliance to the Mediterranean diet, the slower the rate of cognitive impairment.

What I would like to point out, is that no matter whether the person had an apo A2, 3, or 4 genotype, and no matter if they were older or younger, male or female, or Caucasian or African American or of Oriental descent, or whether they had a high education or a low education-when you take all of those variables out and just look at adherence to the Mediterranean diet versus non-Mediterranean diet, what you find is those who adhered by self-compliance to a Mediterranean diet had a much lower rate of appearance of mild cognitive impairment and also had a much lower appearance, later, of Alzheimer's disease as shown in subsequent other studies.

I think these are very interesting concepts that suggest that something is in those diets that may regulate neuronal function through intercellular signal transduction by communicating the dietary principles somehow through the neuroendocrine-immune system to the host through cellular signaling, and ultimately into physiology that is associated with cognitive impairment and later Alzheimer's disease. One of the possible mechanisms-and I don't want to say it's the only mechanism, but certainly one of the possible mechanisms-has to do with the role that insulin plays in cognitive impairment, and how diet may influence insulin signaling, and how that might influence a range of diseases that are associated with cognition and neurological function. We are going to hear more in this issue from one of the world's most well-informed investigators in this area, Dr. Suzanne Craft.

This topic was reviewed very nicely in the *Journal of Alzheimer's Disease* in 2009. The title of this paper is "The Alzheimer's Disease/Diabetes Angle: Inevitable Fate of Aging or Metabolic Imbalances Limiting Successful Aging."⁷ You are going to hear much more of the evidence through the pioneering work of Dr. Craft, but this paper indicates that as individuals consume different diets, it influences their cellular signaling in the neurological regions of their body to then either enhance or decrease things like inflammation, or oxidative stress, or alarm reactions that are associated with accumulation of injury to the neurological system.

Studies of Hibernating Animals Provide Insight on Kinases and Phosphatases

Interestingly, hibernators such as ground squirrels and hamsters demonstrate comparable annual recurrent periods of obesity with concomitant insulin resistance and key features in Alzheimer's disease, such as tau protein phosphorylation. These pathologies, however, are reversed by a time dependent metabolic shift between carbohydrate and fat-based metabolism. This is all regulated by this delicate balance and dance of kinases and phosphatases that regulate intercellular signal transduction. As they come out of hibernation and start eating their traditional diets, this tends to clean out some of the debris that was accumulated in the nervous system during this period of hibernation in which they had temporal insulin

resistance. Massive fat depots serve as the main source of metabolic fuel throughout the winter in these hibernating animals, and phosphorylation of tau protein during this hibernation process seems to be reversible. What we are starting to witness is a sense that maybe the system can move both ways

We have been told that damage to our nervous system (particularly our central nervous system) is kind of irreversible. I recall the old story given to every college-age student that if you binge too much on your Friday and Saturday nights you are losing brain cells and you're never going to get them back again. (It didn't seem to be a deterrent, but it was a message.)

Now we are starting to recognize that even alcohol-induced encephalopathies have some reversibility by getting off alcohol and utilizing nutritional support and regeneration. I think we need to be cautious about what we call "irreversible." Some of these processes may have slow reversibility, but there are still inherent within systems this reverse capability (different cell signaling and cell regenerative possibilities).

This connection of Alzheimer's disease to diet may have something to do with insulin signaling, and insulin sensitivity, and the interrelationship that insulin signaling has to kinase regulatory pathways. These pathways go through things like SYK and Bruton's tyrosine kinase (BTK), and ultimately through phosphatidylinositol 3 kinase (or PI3 kinase) and down in to glycogen synthase kinase 3, which regulates ultimately things like Glut 4 receptor translocation to the cell membrane and glucose transport. All of this also has to do with gene expression patterns and regulating the promoter regions of genes associated with inflammation (there's an inflammation connection to the insulin signaling story). And that then has a role to play in neurological function and proper neurological stability. We are going to learn much more about this, as I said, from the expert, Dr. Craft. I wanted to set the context for her extraordinary work.

We also recognize that there are a variety of phytochemicals that are being discovered that can reduce insulin resistance and improve insulin sensitivity through modulating specific kinases in these regulatory networks. In my own work, I have published studies now showing how a variety of phytochemicals from things like garlic, and various fractions of hops, and berberine, and cinnamon participate in modulation of regulatory networks that are associated with insulin resistance. Dr. Deanna Minich and I published an article that appeared in *Nutrition Reviews* that was called "Beyond Macronutrients" that speaks to this whole discovery and extraordinary increasing understanding of how phytochemicals play this role in intercellular signal transduction.⁸

Berberine is an interesting compound because it has been found and published (both in our work and others') to have a very interesting influence on insulin resistance through modulation of specific kinase signaling pathways that control insulin receptor expression. One such paper was published in 2009 in the journal *Metabolism Clinical and Experimental*.⁹

Epigenetic effects can modulate insulin signaling and neuronal effects and ultimately regulate things that could induce adverse effects in production of neurological injury and neurofibrillary tangles. So things like methylation patterns can have an effect on the neurobiology of disease. This was discussed in an article in the

Journal of Neurosciences about how insulin can influence things like methylation patterns of tau protein and protein phosphatases that are associated with things like homocysteine and Alzheimer's disease.¹⁰

A complex mechanism has been established for us to understand the relationship between dietary signals and nutrients, and how that may translate into neurological function, interconnection with insulin signaling, and ultimately the appearance of cognitive function or dysfunction over years of living. This is a very new view of the potential of pharmacology—a very new view of, in fact, how these whole systems of biology fit together to create what we see at the whole organism as function. It also clearly opens up a mechanistic understanding of back to the future: how what we have learned in the past around traditional diets and complex diets with color and flavor can influence, in their natural ways, health in a positive way. We have made kind of the gross observation that minimally processed, organically grown fruits and vegetables seem to have a positive benefit on health, when we look epidemiologically. But we haven't understood a mechanism of how that really occurs, so people have dismissed it as kind of artifact. But this mechanism of network pharmacology, and kinase signaling, and regulatory networks, and systems biology is emerging now to be the paradigm upon which will rest the understanding of how these things interrelate.

There is no better person I can think of to help us understand this emerging connection, particularly as it relates to insulin and neurological function and how that interrelates with dietary signals than Dr. Suzanne Craft, who is our esteemed clinician/researcher of the month for January 2010.

INTERVIEW TRANSCRIPT

Researcher of the Month

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I've already given you a tip off to the fact that we are going to be having a conversation with Dr. Suzanne Craft this month, but I haven't really said much about Dr. Craft yet (I was holding that for this introduction). She received her PhD in neuropsychology at the University of Texas at Austin, and later fellowships at Boston University and Harvard Medical School specializing in behavioral neurosciences. Currently she is a Professor of Psychiatry and Behavioral Sciences at the University of Washington School of Medicine (which we are very proud of, being here in the State of Washington), and an Associate Director of Geriatric Research, Education, and Clinical Center at the VA Hospital Puget Sound.

Dr. Craft's research team has investigated the relationship between insulin resistance and the development of cognitive impairment and dementia in older adults, which is probably one of the most important singular issues that people are concerned about. I have a mother who is in her mid-80s. When I visit with her and her friends at their retirement facility, I recognize that this seems to be the number one concern that individuals in that age group have. My mom always is very sad when one of her colleagues starts

losing her cognitive function and she starts seeing them slip away. I think this topic that we are going to be discussing is a real-world topic; it's not just a research lab intellectual enterprise. Dr. Craft has done just an extraordinary job in pioneering this field, and you'll hear about her extraordinary work and diligence.

Dr. Craft, welcome to Functional Medicine Update. It's just a treat to have a fellow Washingtonian and a person in this field with such an esteemed background be our clinician/researcher of the month. Let me start off with my first question. I have had the privilege of reading a number of your manuscripts. I think I've read at least all of your papers that have been published since 1996. I would like to mention a paper you authored in 1991 in Diabetes.¹¹ You have made this interesting connection of insulin and blood sugar and how that relates to cognitive function for a lot of years. How did you get started down this path?

SC: First of all, thank you, Jeff-thanks for the invitation to be here; it's a pleasure. I think my interest in neuroendocrinology grew out of the appreciation that changes in cognitive function with aging were closely related to glucose metabolism, I think in a couple of ways. One, of course, is the very well-established finding that patients with Alzheimer's disease have hypometabolism in the brain. They have reduced cerebral glucose metabolism. This can be observed, actually, years before the diagnosis is made. So there is something very fundamental about the changes in glucose metabolism that occur centrally, both with respect to aging and pathological aging, such as Alzheimer's disease.

I think-as many of your audience are likely aware-the brain is unable to synthesize or store glucose, so all of the glucose that it receives for its many functions, it receives from the periphery. The question I began to wonder about was the degree to which disorders that are associated with disrupted peripheral glucose metabolism may potentially impact the CNS, in that the brain may not be able to get adequate supplies of glucose in patients who have such disorders. I think that led me to the study of conditions like diabetes and insulin resistance and how those conditions might affect brain function and cognition.

JB: Recently I know that you were the recipient of what really is a very prestigious NIH award-the MERIT Award-for excellence in your aging research. I actually also caught you in the HBO documentary "The Alzheimer's Project," where you were a principal in describing your work. It seems like there is an interesting paradox. I think you had a paper in 1996 in the Neurobiology of Aging that was about what happened when you gave insulin to Alzheimer's patients and it improved their memory.¹² One could say,, "Now hold it. Isn't elevated insulin associated with hyperinsulinemia, which is like type 2 diabetes and how does this work?" It seems paradoxical that increased insulin improved memory and we might think that that would be not so good for a hyperinsulinemic type 2 diabetic.

Insulin Has Both Positive and Negative Effect

SC: I think the story with insulin, as I describe it, is very much what I consider a "Goldilocks" story. Insulin, one of the most evolutionarily conserved of all peptides, is absolutely essential for a number of functions, and was early on best known for its critical role in promoting glucose uptake, peripherally. Removing insulin, either through a condition such as type 1 diabetes or in genetic models of insulin receptor knock-out transgenic rodent models, is lethal. So I think insulin has many beneficial roles to play. What I think is essential is the appreciation that optimal levels of insulin, in a healthy physiology, have many beneficial effects when insulin is secreted and cleared very quickly in a normal healthy individual (and I think this is the key to its positive effects). When, however, insulin is increased

chronically or is increased to too great of a level, then I think negative effects begin to occur, like the ones that you mentioned, of course-the insulin resistance, where tissues become resistance to the effects of insulin (insulin can no longer carry out its normal functions in tissues), or proinflammatory effects of chronic elevations of insulin. A number of negative effects occur when insulin is too high and around for too long a time. In the studies that we conduct, we're modeling, really, acute insulin challenges, and giving insulin acutely at a level that, again, mimics sort of its optimal effects usually has a beneficial effect on memory.

JB: That is a beautiful segue into a couple of your other papers and earlier publications in which you reported insulin increasing cerebral spinal fluid (A beta 42) levels in normal older adults, and then also report-I think maybe it was even the same year in another journal-as to how those individuals who carry certain apolipoprotein E genotypes may be at higher risk to this insulin-amyloid plaque relationship. Can you tell us a little bit about that? That's an interesting part of the evolution of the story.^{13,14}

The Relationship Between Insulin and Beta-Amyloid

SC: I think a very-as you say-interesting part of this story is the relationship between insulin and beta-amyloid, which of course is the peptide that collects in the brains of patients with Alzheimer's disease and becomes the senile plaques, which are a histopathologic feature-in fact, a defining feature-of Alzheimer's disease. I think it was about six or seven years ago that people began to understand that insulin and beta-amyloid have something of a reciprocal relationship, and insulin can regulate beta-amyloid in several ways, one of which is by increasing its trafficking from within the cell to outside the cell, which is where it needs to be in order to get degraded.

I think the way we conceptualize our studies in which we give high levels of insulin and then we see corresponding increases of beta-amyloid in the spinal fluid, one of the hypothesized mechanisms underlying that effect is that the insulin that we're infusing that then crosses the blood-brain barrier and enters the CNS is promoting the trafficking of beta-amyloid out into the extracellular space in the brain, which then drains, of course, into the spinal fluid. If that were the case, then one could view this as potentially a positive effect of insulin (insulin getting beta-amyloid where it needs to be to be degraded so it can't collect into these senile plaques). And then, interestingly, the enzyme that degrades beta-amyloid (one of the enzymes) that is a key player, is insulin-degrading enzyme, which is a member of a class of metalloproteases that-as its name implies-degrades insulin, but is also responsible in the brain for degrading beta-amyloid. Insulin can affect beta-amyloid through influencing this insulin-degrading enzyme, either by competing for the attention of insulin-degrading enzyme (such that it is not able to adequately clear beta-amyloid), or by regulating levels of insulin-degrading enzyme, so insulin is needed to increase the expression and increase availability of insulin-degrading enzyme.

So there is this reciprocal relationship that exists, and very recent work by Bill Klein at Northwestern has actually revealed a fascinating side to this story in that beta-amyloid appears to be able to affect insulin function through regulating where its receptors are located. When a brain cell (a neuron in the brain) is exposed to beta-amyloid, the insulin receptors move off the membrane into the cell, where they are no longer available to be stimulated by insulin. This very interesting reciprocal regulation between insulin and beta-amyloid I think we've observed in our human studies with the techniques that you've mentioned, with the insulin infusion paradigms and more recently with administering insulin intranasally to get it directly into the central nervous system. Others now are using animal models to try to look more closely at the very specific mechanisms that are underlying the effects that we are seeing in humans.

JB: Can we take that to the next step, talking about the genotypic sensitivity? From your early work ("early" means 2003, in this case, which is not that early-"recent" work, let's call it), it would appear there might be some genotypic interrelationship to some of the sensitivities, so not all genotypes are affected equally by this relationship?

The Significance of Apolipoprotein E in Insulin Sensitivity

SC: I think the best way to describe it is that there is the apolipoprotein E, which is a lipoprotein that is very important for lipid distribution and has been associated with cardiovascular disease for a long time, and it comes in three "flavors" (three alleles) that are designated apolipoprotein E2, 3, and 4. The apo E4 isoform produces a large increase in risk for Alzheimer's disease, so the E4 allele is associated with between something like a two-to-five-fold increase in one's risk for developing Alzheimer's disease across the lifetime.

What we have observed is that when you have a group of patients with Alzheimer's disease, about 50% of them will have this E4 allele. That's a much higher percentage than in the general population. But for the other 50% who do not have the E4 allele, they have Alzheimer's disease, but they do not have a genetic risk factor that, as of yet, has been identified. But interestingly, these patients are much more likely to have insulin resistance. The patients with Alzheimer's disease with the E4 allele do not typically have insulin resistance or, really, a potentially greater level of insulin resistance than the normal population. The way we think about this is that there are potentially two paths to Alzheimer's disease, and probably more than that, but two main paths that we consider, one of which is driven by the physiological processes that are associated with the E4 allele, and then the second major pathway would be driven by factors that are related to insulin resistance.

JB: That is really fascinating. What comes to my mind as I'm hearing you tell that story is knowing that there is some literature (as I recall) that relates high-saturated fat diets with an apo E4 double allele with increased risk to cardiovascular disease in indications of oxidative stress or free radical oxidative injury. It would suggest that maybe there is a diet connection or diet sensitivity to certain macronutrient distributions that might cut across different disease diagnoses associated with the process you are talking about, regulated through insulin and/or other oxidative processes.

SC: I think that's a very good possibility, and the way you've captured it I think is exactly right. That the E4 allele is promoting dyslipidemia and oxidative stress through an E4-related mechanism that I think we are just beginning to understand, and which-also-is likely very vulnerable to the effects of saturated fat in the diet. And analogously, insulin resistance is driving that same pathway, but through potentially other mechanisms that are also vulnerable to dietary influences, so the final common pathway may be these convergent dyslipidemia/oxidative stress effects that interact with beta-amyloid to produce the Alzheimer's pathophysiology, and for one segment of patients they are getting to it through E4, and the other set are getting to it through whatever factors are predisposing them to insulin resistance.

JB: Thank you. That really lines up so consistently with the message that we have been trying to communicate in Functional Medicine Update for many years: that these chronic age-related diseases are not monozygotic diseases. They are polygenic, and there are many different determinants, and to think that we are going to find a gene for Alzheimer's is a little bit like chasing an elusive tail of frustration because there are going to be many different variables that couple together to give rise to sensitivity to

certain environmental conditions that might, over decades of living, be seen as Alzheimer's. That's been our model, and it sounds like what you have said is consistent with that model.

SC: I think so. When apo E (the apo E risk factor) was identified, which was not all that long ago (I'd say it was about 12 to 14 years ago), and then some of the causative gene mutations that cause early Alzheimer's disease were discovered around this time as well, I think the field of genetics felt like they were going to wrap this disease up pretty quickly. But the truth is that those disease-causing mutations only affect about 1% of all patients with Alzheimer's disease (those who tend to get the disease earlier in life) and for the much more common late-onset disease that affects 95% or more of all patients with Alzheimer's disease, we have had very little success.

First of all, we haven't identified any causative genes, and the only gene that has shown consistent, strong relationships as a risk factor is this apo E4 allele. I think the field has, over the last few years, shifted very much to the model that you are suggesting: polygenic, interacting with environmental factors, and the sort of incremental insults, if you will, that occur as a result of a poor diet and an inactive lifestyle causing some cumulative effect and potentially interacting with some genetic vulnerabilities, but in and of themselves having a very great influence on the ultimate expression of a disease.

JB: The way that we have been talking about the etiology of chronic disease recently is to talk about metabolic disturbance through a systems biology impact on gene expression patterns within a network. We are trying very hard to get people to think about networks rather than pathologies and endpoints of a single process. That's a very different way of thinking about disease than most of us were trained to think about it. It is kind of a mind-shifting paradigm. It seems like your work really speaks to that very nicely because it cuts across so many different aspects that we can't just put our finger on one causative agent and say, "That is this disease."

SC: I think that's very true. Even though my work has focused most closely on hyperinsulinemia and insulin resistance, that, in and of itself, is a system that affects so many different other systems that it is, by its very nature, a pleiotropic model, even though we are focusing on a single peptide as a key player in that ultimate web of causation. Absolutely, and that very much drives a different approach to therapeutics, I think-very much away from the "silver bullet" days of the cholinesterase inhibitor or the single molecular target as likely to be the therapy that will prevent or cure Alzheimer's disease and moving more toward therapies that do have these pleiotropic effects on the systems that we now know are greatly increasing the risks of developing Alzheimer's.

JB: We're calling that "network pharmacology." It is interesting that if you look historically, that's probably the way physiology has worked-as network interaction with our environment--throughout time. When we eat, we are eating complex molecules in our diet that influence, in a network pharmacological way, gene expression patterns that modulate function. It's a whole different model, which then leads me to what I consider one of your landmark articles. To me, when I read it I just lit up. I thought it was beautifully written. It is your review article on "The Role of Insulin Resistance in the Pathogenesis of Alzheimer's." I think for many people, until maybe they read your article or heard about it, they might have thought about diabetes and Alzheimer's as it related to Type 1 insulin deficient diabetes, but they may not have thought about insulin resistance, the more predominant problem that we are encountering in our society now with metabolic syndrome and so forth. I'm sure all of your colleagues didn't rush to just

say, "Yes, that's exactly right, what you've got there." There must have been some controversy.

SC: Absolutely. I think for a long time this idea was very much considered on the fringe of possible important factors. I think what has really happened, again, over the last 10 years is the good epidemiology has definitely helped to point the field in the direction of metabolic factors as potentiators of Alzheimer's pathogenesis. The idea that hypertension, and hypercholesterolemia, and diabetes...for awhile they were considered risk factors for vascular dementia, or for dementias that were what used to be called multi-infarct dementia. I think what has happened, with very good epidemiology, is it has become clear now that these conditions are risk factors for Alzheimer's disease as well as for vascular cognitive impairment or vascular dementia. I think diabetes is a very easy disease for people to focus on. It's very common. It's very easy to understand. It's defined very glucose-centrally. And I think what that did for awhile was that that did help raise awareness within the field of this class of factors as important, but I think now the progress is being made in understanding that the underlying these various conditions there is, in many cases, a convergent pathophysiology, which is insulin resistance.

Insulin resistance, of course, is associated with nearly all cases of type 2 diabetes. Insulin resistance is observed in about half of all adults with hypertension. It is a main cause of dyslipidemia. Instead of viewing each of these vascular risk factors as independent or able to drive the Alzheimer's pathogenetic pathway independently, I think we are now beginning to understand that there is an underlying convergence which focuses around insulin resistance and hyperinsulinemia.

You're right, that was not well-accepted as a potential mechanism when I first started studying this a number of years ago, but I do think now the field is much more receptive and good basic science work is really also helping now with some of the studies that I just described linking insulin and insulin resistance to beta amyloid and other pathogenic agents that are well known to play an important role in the expression of Alzheimer's.

JB: In your review, you raise some really interesting questions about modulators. I guess you might even call them in the human "reducible risk factors," like HPA axis function, which we think of as related to how we are interpreting our environment and translating it through the neuroendocrine system into hormonal messages. Some people might even call these the stress/Selye mechanisms and how that relates then to insulin sensitivity. You've talked about the role that various nuclear orphan receptors have and how that regulates things like inflammation and signals over into vascular effects through PPARgamma and how that might have some effect. You are really laying out, in this article, I think, a very interesting different way of approaching pathophysiology from a-I guess I would have to use the term that we use-a "functional perspective" by looking at these modulators of function that then ultimately trigger processes that distort the web of physiology and produce what we ultimately see under the microscope as amyloid deposition.

SC: I think that's true. I do think when people begin to sort of appreciate the complexity of this web it is daunting at first. I think somebody has referred to it as "the morass of intermediary metabolism" or something like that because these effects-these modulators-are interrelated, but in a sense, I have come to view that almost as a positive aspect because I think it offers many portals for intervention. The truth is that intervening at one level of this web may likely have beneficial effects at many levels. I think an example of that might be the fact that certain treatments for hypertension protect against diabetes, and certain treatments for diabetes protect against hypertension. One might not have to be able to address the

initiating cause, if you will; it might be enough to be able to find an intervention that can affect a number of these modulators and have a beneficial effect on the whole web.

JB: I think you really stated that beautifully. As you are speaking I'm thinking in the back of my mind about the group that has been looking at bisphenol-A's influence on insulin resistance and the relative risk to cardiovascular disease and diabetes, or the work that has been done on persistent organic pollutants (POPs) and their elevation of GGTP liver enzyme profiles and how that relates to insulin resistance and diabetes and how that could connect to the brain through this pathway that you are describing-through hyperinsulinemia, through what appears to be a distant effect, rather than just looking at the body as a collection of organs that are all isolated and compartmentalized. They are all interconnected through these pathways of signaling.

SC: I do think that's a clear message of this work and I think that is part of why it was difficult to make progress for a number of years because I don't think that the neurologists think much about below-the-neck systems, and I don't think that the endocrinologists think much above the neck (or at least above the hypothalamus). I do think this is an example of the way in which the central nervous system and the periphery are closely interrelated. I think each is capable of driving these pathologies, so an example would be the one that you cited where the exposure creating insulin resistance would affect the CNS, and then conversely we know that when there is insulin depletion specific to the CNS, or insulin inactivation that originates in the CNS, you get a compensatory increase in insulin secretion in the periphery. Beta-amyloid, as I said, is capable of causing brain insulin resistance, if you will, and that may drive insulin resistance and hyperinsulinemia in the periphery.

JB: That leads me, then, to a series of papers that you have published that I think are-again-so interesting and provoke all sorts of thought. They have names like "Hyperinsulinemia Provoking Synchronous Increases in Central Inflammation in Beta Amyloid and Normal Adults."¹⁶ This is looking at things like increased isoprostane levels and cytokine levels. And a companion paper: "Insulin Resistance in Alzheimer's Pathogenesis: Potential Mechanisms" that talks about the inflammatory connection.¹⁷ And then in the Journal of Neurological Sciences, your paper "Insulin Resistance, Inflammation, and Cognition in Alzheimer's Disease," and you had the-I guess you call it-temerity or the boldness to then even have in that title "Lessons for Multiple Sclerosis," God forbid that we cut out to another disease now with a similar mechanism.¹⁸ (I said that tongue in cheek, obviously.) These are really pioneering papers that when coupled together give rise to a body of knowledge that creates a different system of thinking about the etiology of diseases that fan out from a mechanism rather than just each individual disease being siloed. That's how I read these papers.

SC: Again, with insulin being a peptide with such pleiotropic effect, I do think that it is related to a variety of types of neurodegenerative disease and CNS inflammatory states, and then the challenge becomes to determine why in one patient it might be associated with Parkinson's disease and why in another patient it might be associated with Alzheimer's disease. Is it insulin resistance driving some innate vulnerability otherwise determined, or are there types of insulin resistance? We know, of course, insulin resistance is a very heterogeneous condition, and so I think that is now one of the main challenges: to try to determine what particular mechanisms associated with insulin resistance may drive these different pathological pathways. Certainly inflammation is a set of responses common to a host of disorders. Almost anything that negatively impacts the brain is going to provoke some kind of inflammatory response. And the interaction of insulin resistance with inflammation, I think, is another complex topic. We are beginning to

understand that insulin, in some ways, has anti-inflammatory effects. Again speaking to the issue of relatively lower levels and relatively confined time frame, when insulin becomes chronically elevated segues into a more proinflammatory response. So these are complex questions that will keep us busy for some time to come.

JB: If our listeners want to pick out a recent paper of yours that kind of puts this together very beautifully, I think your review paper that you authored titled "The Role of Metabolic Disorders in Alzheimer's Disease and Vascular Dementia: Two Roads Converged" that appeared in Archives of Neurology in 2009 is a very great place for people to start.¹⁹ I think it really is the most concise, extraordinarily well done summary of a large body of work (yours and many other investigators) that helps a person who is getting into this for the first time to understand the field.

In our last few minutes together (obviously this conversation could go on ad infinitum, as far as I'm concerned, but with time being what it is...), could you tell us a little bit about whether you feel (and I think I know the answer to this question), from your discoveries, this opens the door for one of the therapeutic approaches towards these problems in the arsenal of tools being diet modulation? I am reminded of the epidemiological work of the patients that has been done on patients who comply voluntarily to Mediterranean diets versus those who eat a standard American diet and their rate of dementia over 10 years and their rate of mild cognitive impairment-those are published papers over the last few years. It would at least suggest, from epidemiological work, that diet probably has some role to play in this whole process.

SC: I think that's absolutely the case. One of the studies currently underway that we are just about to complete looks at that very question. Studies in which you query people about what they are eating and then relate it to aspects of dementia risk can be informative but suffer from not being able to control aspects of diet specifically. What we've done in a study that is going on now is we have participants who are either normal older adults or adults with very early cognitive changes characteristic of Alzheimer's disease undergoing a dietary intervention where they receive 30 days of a high-fat, high-glycemic-index diet or a low-fat, low-glycemic-index diet. Before and after this 30-day period we're carrying out a number of measures, including looking at their spinal fluid markers of inflammation and beta-amyloid, and looking at some changes in neuroimaging. We are attempting to address this very question.

One of the things we are trying to do is model the early stages of diet-induced insulin resistance in a manner that's very safe. We see, in our participants, all of the characteristic beginning changes of insulin resistance in terms of increased LDL, increased insulin levels, and all of these revert back to normal within just a couple of weeks after patients come off their diet. And interestingly we also see improvement in the folks on the low-saturated-fat/low-glycemic-index diet. One of the things we hope to do with this study-and we have been fortunate enough to be funded already by NIH to do the next version, so we're going to continue on with this work-is to see how these very beginning changes in insulin function can provoke some of the pathological changes that we know happen with Alzheimer's disease, and also to see if our patients who are already showing some signs of cognitive changes are particularly vulnerable to this dietary intervention. We're thinking very much along the lines of what you've described. We're just hoping to develop a controlled experiment that will, in a very safe manner, give us specific insights into how the diet is relating to the Alzheimer's pathology.

JB: Unfortunately our time has come to the end. I want to, once again, personally congratulate you. I

think this is both pioneering and courageous work. This is not the easiest work and you are going uphill, often, against this dominant view that each disease is independent, one from the other, and we have these siloed effects. You're really talking about a systems biology approach using a signaling molecule that has pleiotropic effects (insulin), and it's cutting across a lot of different subspecialties of knowledge, which always makes people uncomfortable (when you step on turf). There are a lot of things you have done very, very well as a scientist, and I'm sure also done well as a scientific politician because you've had to orchestrate through some sticky wickets and you've done it very well. I compliment you, and this is the kind of work that is going to change medicine for the better. We have an age-related burden of disease that is epidemic right now with our demographic transition. We need to find new solutions and this kind of work will help us do so. Thank you very, very much-both as a son of a mother who is growing older, and as a person who is also growing older, and for a generation of people who are trying to find better solutions to complex diseases.

SC: You're very welcome, Jeff, and thank you again for the opportunity to speak with your audience today. It was a pleasure.

JB: My pleasure. Thanks so much, Suzanne.

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