October 2014 Issue | Philip Kern, MD

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I'd like to welcome you to an exciting month of *Functional Medicine Update*. This is the first in what we will have as a three-part series on this advancing epidemic that we call insulin resistance, type 2 diabetes, metabolic syndrome, hyperinsulinemic-driven health issues. And as you probably recognize, this is the issue of our age. It's the metabolic disease age that we live in as a consequence of the messages that our genes are getting from our environment—our diet, our lifestyle, our stress patterns, things that are being exposed to us as a consequence of the chemical industry which now are being recognized to have subtle effects on mitochondrial bioenergetics, which is a form of internal energy production that relates to things clinically like insulin sensitivity and glucose transport and the ability to process and utilize energy effectively in the body. This concept of insulin resistance, type 2 diabetes, hyperinsulinemia is a very, very interesting concept related to the functional medicine model, because what we're observing is a transition from a view that a disease is caused by a specific singular mechanism, or a specific singular infection with an organism, to this pleiotropic model—this model where there are multiple different routes to get to the same disease that we call a diagnosis, and in this case the diagnosis is often type 2 diabetes. But the route by which a person got to that diagnosis may be very different from individual to individual.

So this month, which is the first in this three-part series reviewing this extraordinarily important area, both where it comes from and what to do about it, we're going to have the opportunity to hear from Dr. Philip Kern, who is an endocrinologist of repute, respect, and highly published. As you will learn, he is head of a diabetes research institute as well as a diabetes and obesity clinic at the University of Kentucky, Lexington, School of Medicine. He is a person who is going to help us set the tone for understanding the endocrinological challenge that the rising spectrum of insulin resistance and type 2 diabetes is presenting to the medical system. And I think one of the things we'll take away from this is that there are varying degrees of concern as it relates to this spectrum of disorders. At the extreme edge are the clinical signs that occur with fulminant type 2 diabetes, such things as neuropathy, nephropathy, retinopathy, liver failure, kidney failure. These types of very acute illness situations present in the extreme edge of the type 2 diabetes or the type 1 diabetes spectrum. In the earlier stages, however, the signs and symptoms of presentation are much more subtle because they don't ring out so clarion as a pathology. They may be things as cognitive dysfunction. They may be seen as obesity. They may be seen as hypertension. They may be seen as chronic kidney-related dysfunctions. They may be seen as immunological dysfunctions. They may be seen as a host of cardiometabolic signs and symptoms, including dyslipidemia.

Global Health Shifts Due to Changing Lifestyles, Socialization, and Environment

So it's not easy just to pinpoint a specific target presenting sign and symptom when we're talking about this wide spectrum of conditions that are under the umbrella that we call insulin resistance, type 2 diabetes, and hyperinsulinemia. As it pertains to the prevalence, I think there is no doubt that we see this as a rising tide—almost an epidemic or a pandemic—that's not only seen here in the United States, but we've exported this now, with the Western lifestyle, to many other countries in the world, including what is the country of greatest concern right now as to type 2 diabetes, which is China.

Twenty years ago, type 2 diabetes was virtually unheard of in China. It was a disease that was only seen in the United States with great prevalence, and now it is starting to be recognized as an epidemic in China. And as a consequence, people have asked, "Well, how could this occur?" The Chinese genotypes haven't changed so dramatically in 20 years. What has changed, obviously, is the industrialization, socialization, diet, and lifestyle patterns, which, in the Chinese genome, there are sensitivity or susceptibility factors obviously that are being presented through the phenotype as a consequence of the adoption and the uptake of the Western lifestyle. And so this is almost a laboratory experiment without a control, and that is what we're observing is a self-elected study on how to get a culture to transition from a disorder that didn't exist to that which becomes the standard of fare for the average person to become diabetic as a consequence of changing lifestyles, socialization, and environment.

So I think there is much to learn—much to be also concerned about—if we were to go to the United States as a model study and look at the prevalence of type 1 and type 2 diabetes among children and adolescents. We used to think of type 2 diabetes as being adult onset diabetes. That was the name, but it had to be changed into type 2 because there were so many adolescents and children that were starting to present with this condition. So if you look at the prevalence of this condition from 2001 to 2009, what you see is virtually a hockey stick of exponential increase, and I'm now quoting from an article that just appeared recently in the *Journal of the American Medical Association* titled "Prevalence of Type 1 and Type 2 Diabetes Among Children and Adolescents From 2001 to 2009."[1]

What I found to be interesting and I didn't recognize until reading this article in greater detail, is that type 1, which we used to call juvenile onset and we considered it to be kind of a tightly genotypically inclined disorder, it is also increasing significantly, and we recognize that type 1 diabetes is associated with an autoimmune disease of the islet cells of the beta cells of the pancreas, and therefore whatever it is that is initiating this autoimmune insult to the children's own endocrine pancreas is on the increase. It's not that their genes are increasing, something in the environment, or some things, obviously, are triggering increased autoimmune response of the child's immune system to their own pancreas, killing their beta cells, making them insulin requiring. And I think that this insulin-dependent type 1 diabetes phenomenon really ties together the autoimmune condition with the metabolic disease condition, and I believe that this is a topic that we'll be discussing in greater detail throughout the course of this three-part series on insulin resistance and metabolic syndrome/type 2 diabetes. That there is ever-increasing understanding that these metabolic diseases are tightly tied to our immunological disorders (the autoimmune family of disorders), or what used to be considered as the body allergic to itself.

Immunological Disorders Do Not Result From the Body Becoming Allergic to Itself

I think that is, by the way, a very false misnomer. I don't think the body becomes allergic to itself. I think what happens is our immune system of certain individuals becomes hyper-reactive to foreigners that are produced within the body, and these foreigners are foreign molecules that have come from the damage of cells and tissues or biomolecules that then present themselves within the body as an endogenous foreigner which then the immune system responds to by producing an antibody reaction or cell-mediated reaction. This is the innocent bystander response where you start getting collateral damage to the tissue itself because the body is actually responding to this perceived foreigner in such a way that it's found in situ within tissues, and the tissues become the secondary outcome of the body's defensive system that's trying to handle a mischievous foreigner when the foreigner looks like it is part of us. So I think that this concept that we are allergic to ourselves is misleading because it leads us into a circular reasoning saying, "Well, there's nothing we can do about being allergic to ourself because we are ourself so what are we going to do?" In this case, however, is, "It's not really ourself, it is something that has transformed ourself into a foreigner, or at least a portion of ourself into a foreigner, for which our immune system, which is unique to each one of us, responds in a unique way to start attacking that foreigner.

Let me give you an example that we'll be discussing in greater detail in the subsequent parts of the series, and that is glycosylated proteins. We recognize that one of the hallmarks for following diabetes is hemoglobin A1c, or glycosylated hemoglobin. And this is where the hemoglobin molecule has been non-enzymatically glycated, meaning that glucose has reacted in a specific type of chemical reaction in the aldose form of the glucose molecule by reacting with the epsilon amino groups of lysyl residues on hemoglobin to produce these shift spaces. So what we're really saying is that there is a covalent chemical connection then between glucose that ties itself onto hemoglobin and makes a funny hemoglobin. That's not the natural hemoglobin; it's now a modified hemoglobin. So that becomes a foreign molecule.

We then measure glycosylated hemoglobin as a percentage of total hemoglobin. We say that people that have glycosylated hemoglobin, or hemoglobin A1c greater than seven-and-a-half to nine percent of the total hemoglobin are people with glucose intolerance and they are diagnosed as diabetic. But in the form of the body's immune system we say the increasing prevalence of these glycosylated hemoglobin molecules floating around in our blood means the presence of more foreigners, and so at a certain point, our immune system, based upon our own unique genotype, can say, "Oh, just a minute. There are all sorts of these hemoglobin foreigners that are floating around in my blood, I need to form an antibody against them, or I need to form a reaction."

Now, it's not just hemoglobin that gets glycosylated. Virtually every soluble protein that's floating around in the presence of excess sugar in the blood can be glycosylated, so what's the most significant protein in the blood? It's albumin. So can albumin become glycosylated? Of course it can, so now we get

glycosylated albumin. Well, that's a foreigner. And so now the immune system says, "Oh, here's another foreigner. Maybe I'll form an antibody to that foreigner." And so forth and so on.

The point I'm trying to make is the more that we have modified our body through certain kinds of chemical reactions with either internal molecules like glucose, or external molecules like foreign chemicals that we absorb or ingest, the more likely that our immune system may have a reaction to those foreigners, producing, then, damage to specific tissues. And if those reactions happen to reside within the beta cells of the endocrine pancreas, now what we see is apoptosis (or death) of those beta cells. And as they get depleted, that means less cells available to secrete insulin, and less cells available to secrete insulin mean we become more sugar sensitive and we eventually get to the point where, in the type 1 diabetic, we need insulin in order to maintain control of the blood sugar at all.

Genotypic Susceptibility to Type 2 Diabetes

And so this article in the *Journal of the American Medical Association* in 2014 does a very nice job of describing both the increased prevalence of type 2 diabetes, but also of type 1 diabetes among children and adolescents, suggesting that there are common features that are associated with both of them. Now there are specific genetic types that appear to be emerging to have greater susceptibility or sensitivity to some of these derangements that I'm talking about in internal cellular milieus—some of the alterations in various molecules that come through these metabolic networks. We can't say that there is a single gene that causes type 2 diabetes, because type 2 diabetes is not a single disorder. It's all these different things that cluster together to give rise in a person to the inability to manage sugar well in their system.

Now there are a couple of interesting papers that have appeared recently talking about genotypic susceptibility, again showing that there are many genes probably that give rise to different responses that we would ultimately see as mutant genes that could increase the relative risk of type 2 diabetes. One is mutation of the gene DYRK1B, which has been found just recently to, in a mutated—what we would call SNP form, single nucleotide polymorphic form—to be conferring an increased susceptibility to both metabolic syndrome, meaning hyperinsulinemia/insulin resistance, and then later type 2 diabetes. This appeared in the *New England Journal of Medicine* in 2014, volume 370, page 1909.[2] What they found, looking at various kinds of genome-wide association studies, was that there was an early-onset coronary artery disease profile that related to hyperinsulinemia, this is what would be called cardiometabolic disease, where there is a heart disease risk that's associated with the insulin resistance that was tightly tied to this mutation of DYRK1B, which is involved with the regulation of the key gluconeogenic enzyme glucose-6-phosphatase. Here is just one example, and I don't want to go into great details about that other than to say this is one recent example of where a gene controls a susceptibility factor. It doesn't confer the necessary outcome called diabetes, only under certain specific kinds of environmental conditions does it express itself, then, into a diabetogenic form.

Another example of that is a paper that appeared again in the *New England Journal of Medicine* looking at PTEN mutations as a cause of constitutive insulin resistance and obesity.[3] Again, another gene controlling an activity that relates to regulation of sugar and how that then attracts itself against ultimately increased increasing risk to type 2 diabetes, metabolic syndrome, and obesity. Here is where we start looking at the PTEN monogenetic cause of constitutive insulin sensitivity and how that relates to obesogenic effects that ties together the insulin connection to obesity—that when you have dysfunctions in insulin sensitivity, you have derangements in energy economy, you have adipocyte functional changes, and you have more storage of fuel (the energy that we take in from our diet for a rainy day that never comes), and so people tend to get central adiposity. Their waist-to-hip ratio increases. This doesn't mean that obesity causes diabetes, it means it comes as a consequence of these metabolic derangements. So obesity is an effect, not always a cause of diabetes. They come together as a consequence of disruptions in the metabolic network that regulates sugar metabolism.

So I think that these are themes that you're going to be hearing in greater detail that we'll be discussing in the subsequent issues of this three-part series on insulin sensitivity, type 2 diabetes, metabolic syndrome, and cardiometabolic disease. And with that, let's move to our extraordinary expert who will lay the groundwork for us from an endocrinological perspective, as to what is this field of diabetology all about in the 21st century?

INTERVIEW TRANSCRIPT

Clinician/Researcher of the Month

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Once again we're at that portion of Functional Medicine Update that really drives, I think, the interest and the currency and really makes the news-to-use happen, and that is our clinician or researcher of the month section. We're very fortunate this month that we have a person that I think fulfills the bill on both

of those accounts—both as a clinician (endocrinologist) by training and also an extraordinary researcher in the field of obesity, diabetes, insulin resistance, and the attended effects that occur with diabetes. I'm speaking of Dr. Philip Kern, who is a professor of the Division of Endocrinology and Molecular Medicine, Director of the Barnstable Brown Diabetes and Obesity Center, and is engaged at the Center for Clinical and Translational Sciences as its director.

I had the privilege of going out to Lexington, Kentucky to visit for a day with Dr. Kern at the University of Kentucky Medical Center and had a chance to really explore the breadth and also depth of his expertise, both as a clinician and as a researcher. His publication record is stellar. We're going to dig into some of the newest stuff—what I call news to use—getting a little bit into the discussion of beiging of fat and how it turns into brown fat and all these new things that are starting to help us understand better the role of the adipocyte in health and disease.

Dr. Kern, what a privilege and pleasure to have you as a clinician/researcher of the month on Functional Medicine Update. Thank you.

PK: Yes, thank you. It's great to be here.

JB: Let me start just with your clinical side of the house, here, for a second, knowing that you're a regional center at Barnstable Brown Diabetes and Obesity Center for patients with those kinds of clinical conditions. What's your clinical observation concerning the prevalence of type 2 diabetes and that we're told that diabetes is growing to be more than ten percent of our population as a diagnosable disease? I remember in school in the sixties we were told it was three percent and would never change, and certainly there are things afoot. What's your observation as a clinician as to what's going on in this domain?

Perceptions About Diabetes Have Changed Over the Last Several Decades

PK: Yes, the obesity epidemic, of course, is making us all look silly in terms of predictions that might have been made some time ago. Once upon a time we used to define diabetes in terms of juvenile diabetes and adult diabetes. Those terms are no longer used, and they are no longer used for a variety of reasons, but one of which is that type 2 diabetes—the kind that is driven by obesity and insulin resistance—is now being seen in children. Of course it has always been known that type 1 diabetes can actually occur in adults, but our pediatric colleagues have now had to learn quite a bit about type 2 diabetes because they're treating it all the time.

JB: So I think the takeaway, just to make it simple, is that this condition that was maybe previously—at least in my education in the sixties—was considered principally a genetic disease has taken, now, a variation of a theme in which we see the environment playing a pretty important role.

PK: Yes, it is highly genetic and that's very true. In fact many people don't realize that type 2 diabetes is actually more strongly inherited than is type 1 diabetes. Some people seem to mistakenly think that type 1 diabetes is "the severe diabetes," and it is in that they require insulin. But type 2 diabetes is strongly inherited, but it is genetic and environmental interaction. Obesity tends to drive the process in people with appropriate genetic background. And the genetic background, of course, is very common. There has been a lot of research into the genetics of type 2 diabetes. It is very complex. There is not "a" gene; there are many, many different genes that are involved with type 2 diabetes, and in fact probably many of us have

some combination of these genes. So if a very large segment of the population has some genetic predisposition to type 2 diabetes, then all you need is an insult like obesity to start driving the process to very high percentages.

JB: So for our clinicians, as a quick review, what are the companion issues that you see that are of greatest concern that ride with this obesity/diabetes epidemic?

Obesity is a Risk Factor for Many Diseases Beyond Diabetes

PK: Well, obesity causes many problems. In addition to diabetes, there is the sleep apnea and hypertension, which all, of course, tends to promote cardiovascular disease. The wear and tear on the joints, and so our orthopedic colleagues are doing more knee replacements and hip replacements because of just the extra wear and tear on the joints from carrying the excess weight around. And then, of course, diabetes has downstream effects on kidney disease and eye disease, and so there are many, many different medical problems that are all flowing from this. And heart disease is, of course, the ultimate medical problem that causes premature mortality and death. So on the one hand, we have made great progress throughout the decades in cholesterol-lowering medications, antihypertensive medications, coronary care units and other systems that help save lives of people with coronary disease, but on the other hand we have this obesity epidemic that is causing all these risk factors: the diabetes, and the lipids and hypertension, and other things. So it's this perfect storm, in a bad way, that seems to be making coronary disease worse.

JB: I recall reading recently a number of papers that have been talking about cardiac disease associated with diabetes and I think, as I recall, some of the conclusions of these studies were that very tight control over blood sugar levels didn't seem to relate to the reduction in incidence of cardiovascular disease, suggesting that there wasn't a direct linkage between blood sugar and cardiovascular disease. What's the story on that emerging front?

PK: You're right. It's a complex story, however, throughout the years there have been many studies that have tried to examine the relationship between glycemic control and coronary disease. One thing that is very important is that improving glycemic control certainly does not reduce the incidence of coronary disease as well as. One thing that is very clear is that improving glycemic control certainly does not reduce the incidence of coronary disease as well as does, for example, lipid lowering, or antihypertensive treatment. And there have been a lot of negative studies. There are a couple of caveats to that. Now there was one study—the UK PDS study, some years ago. It was a complicated study that there was a signal to suggest that maybe coronary disease was reduced in that study. And then in the Diabetes Prevention Program trial, which was a study with type 1 diabetics where they randomized type 1 diabetics to tight control versus intermediate versus poor control, that study completed, but even looking downstream years later from that study, there was a suggestion that the previous tight control had an improvement in coronary disease. But then on the other hand there are other studies, like the ACCORD study. ACCORD took type 2 diabetics, and many of these type 2 diabetics had a full court press done on them to get tight glycemic control—multiple medications getting their A1c down to 6.5 range or even lower, and actually they saw an increased incidence of coronary disease and coronary death in these patients.

We're at a point right now where we feel that with type 2 diabetics, when you are trying to improve glycemic control, the main reason you're trying to improve glycemic control is to prevent the

nephropathy, the retinopathy, the neuropathy. You might improve the triglyceride levels and the HDL levels in these patients, but if your real goal is to reduce the likelihood of coronary disease, then you really need to focus on lipids, hypertension, and other cardiac risk factors, and glycemic control by itself is probably not going to be a strong means of reducing coronary risk.

Are Peripheral Neuropathy and Retinopathy Reversible?

JB: That's a very good bit of clinical news-to-use. Thank you. Let me speak with you just for a moment about the chronic renal disease, the peripheral neuropathy, and the retinopathy issues. If an individual gets their blood sugar under control and drops their A1c down to a level at or below 6.5 percent, what I always heard was renal disease, or chronic renal injury, or peripheral neuropathy, or retinopathy are irreversible. Is there any evidence that one can rolel back or improve function, or is it just preventing the increase in dysfunction?

PK: It's mostly a stabilization of the process and preventing further progression. There is evidence that once the nephropathy gets to a certain point, that point would be when the creatinine is clearly elevated to 2 or more, when there is significant nephrotic range proteinuria. At that point it is very clear that the renal disease is going to progress. Now if you are at other stage, where the creatinine has not elevated yet but you have microalbuminuria (so there are trace amounts of protein or albumin in the urine), that stage is still amenable to tight glycemic control and slowing down the process with, of course, ACE inhibitors and other antihypertensive treatment. I think the farther the disease progresses, the less likely it is to stabilize or reverse with tight glycemic control. Same thing with ophthalmopathy. By the time you need laser treatment for your eyes, then tight glycemic control still may be important to prevent further eye disease, but you're still going to need the laser treatment; the die has already been cast and there is only so much you can do.

JB: That then obviously raises the question as to how do we get good, early interrogation so we can intervene before we have this irreversible pathology. You've talked about two analytes, one being A1c and the other being urinary microalbuminuria. Are either of those, or both of those, useful tools in early assessment of changes so one can intervene more early?

Patients Should See an Endocrinologist Once a Year

PK: Yes, and that's one of the important roles for the endocrinologist. I have a lot of respect for the general practitioner, the family medicine or internal medicine doctor, or the pediatrician, because when you're seeing a patient you've got a lot of things to think about in terms of prevention. And then when you add diabetes to all this, then there is other preventive measures, and so typically you follow the A1c as a great indicator of glycemic control, you want to get a urine microalbumin once a year, the patient needs to get their eye exam. You need to look at their feet periodically just to make sure there are no lesions on their feet. You need to do testing of their feet for sensation. There are a lot of things that need to be done. I encourage our generalist colleagues—our family medicine and internal medicine doctors—maybe to send their patients to the endocrinologist maybe just once a year for a check-up so all these boxes can be checked just to make sure that everything is optimized. I think that's a very good system for trying to prevent diseases before they occur.

JB: So let me speak briefly with you about the A1c. I recently read a couple of papers saying that this

driving to lower A1c, which is a desirable objective, you can drive A1c too low—that the curve turns the other way and you start seeing increased incidence of vascular and other diseases with too low an A1c, presumably maybe as a consequence of hypoglycemia. Any evidence, in your experience, on that curvilinear relationship of A1c, say, below 5?

PK: Yes, there is some evidence. A lot of it is a little bit speculation. Now a lot of this comes from the ACCORD study, as I had mentioned before. The ACCORD study was a very ambitious study in type 2 diabetics to look at a full court press on glycemic control, lipid control, hypertensive control, and what they found is that sometimes that full court press actually results in increased mortality.

Now exactly why was there increased mortality? That has not been totally clear. There is speculation that some of these patients may have been having hypoglycemic episodes, and so if you have an older type 2 diabetic maybe with some coronary disease (coronary disease may not be clinically apparent but it may still be there), and if you are provoking frequent episodes of hypoglycemia, then that hypoglycemia produces catacholamines and will put a stress on the heart and perhaps could result in an MI or sudden cardiac death or some other adverse event. So that's the speculation. And I think anecdotally, clinicians have seen this. We've all seen patients who did have some kind of an adverse event of hypoglycemia, but it's hard to make that conclusion precisely from the study. So my take on this is I think as clinicians we should use our clinical judgment.

Examples of Clinical Judgment

So I see a patient in the office, for example, and this patient is on ten different medications. They are on a medication or two for their lipids, for their diabetes, their hypertension, for their coronary disease. They may be on an antidepressant. They may be on something for their bad back. They may be on a proton pump inhibitor for their stomach. You do get the picture; they are on a lot of different medications. And so they come in and their A1c is 7.5, and their blood pressure is 140/85, and their LDL is 130 or 120. Basically, there are a lot of different things that could be better.

So what do I do? Do I start pumping up the blood pressure medicines and the cholesterol medicine and the diabetes medicines? Or do I focus on one or two and maybe saying, "Well, let's save the other ones for another day?" This gets into a medical judgment. In the ACCORD study, you'd pump up the insulin; you'd do everything. But in real life, I think often we tend to choose the battles that we're going to try to achieve in this particular patient. So we may focus on the blood pressure and the lipids and to say, "Let me just leave the A1c at 7.5; it's probably good enough." And I think that's kind of where we are right now with A1c and especially in type 2 diabetics, is that there is a certain point where it's probably good enough and we don't need to make it perfect.

JB: Thank you. That's very insightful. If you were to pick a range as to what you think is an optimal A1c, is there a range that you would feel would be a good target?

PK: Well, an A1c of 7.5. Below 7.5, you probably will improve microvascular disease—you know, nephropathy and retinopathy—by going below 7.5. But you'll get much more bang for the buck going from 9.5 to 7.5 than you will from going below that. I tend to focus more on getting people down to 7.5. Below 7.5, it depends on the circumstances. It partly depends on who we're dealing with. Now, if the patient is 75 years old and already has, say, coronary disease, then why am I trying to get below 7.5?

Because the person is probably not going to live long enough to get nephropathy or retinopathy. On the other hand, if the patient is 38 years old and is relatively free of complications, then I can focus more on prevention and then I may want to get that A1c down to 7 or 6.5 or 6.8 if I can do it without significant side effects, because then there is a real opportunity to prevent disease in the future. So I think you have to individualize it to who the patient is, what the comorbidities are, and what your long-term objectives are.

JB: Let's say I had a patient that came in and they had a fasting blood sugar, on average, in the morning, of somewhere around 115, 120. Let's say their A1c was something like 6.9, 6.8, something like that, percent. And you were putting them on a lifestyle intervention program before you were starting to medicate them. Would you try to get a target A1c (in that case you're kind of in a pre-diabetes situation), down into the 5s, or would you be more moderate in your objectives?

PK: Yes, you're absolutely right. The optimal intervention would be lifestyle in a patient like that. Now if that patient had a fasting glucose of 120 or so, but then the A1c is 6.9, so the A1c is in the range of diabetes; the fasting glucose is not quite diabetes. But whether you label that person as diabetes or impaired…you would probably label them as diabetic if you look further. But regardless of how you label them, if that person is overweight or obese, and if that person loses even a modest amount of weight, it's very possible that the blood sugar will totally normalize, and so you really want to emphasize that very strongly and have a program hopefully that they can go to help them out with this.

On the other hand, in that same patient, if that patient had, say, a triglyceride of 400 and that patient tells you they have a strong family history of heart disease or maybe the patient has heart disease, then you might have some secondary objectives that you might want to shoot for: treating lipids, and you might want to become more aggressive with lifestyle, and you might choose to use a medication in that patient earlier than you would in somebody else.

So I think doing a little bit of office genetics—trying to assess the patient as to where they are going. Is this a generally asymptomatic "healthy" person with an A1c of 6.9, or is this someone who is a train wreck waiting to happen with an A1c of 6.9. Sometimes that will help push your treatment one way or the other.

JB: Yes, that's very, very helpful. A number of years ago we had the privilege of interviewing Dr. Suzanne Craft, who was at the VA and at the University of Washington School of Medicine, who had been doing some work on Alzheimer's dementia related to insulin resistance and diabetes and came up with a concept called—I think she or someone else termed it—"type 3" diabetes. What's your view of this connection between dementia and diabetes and hyperglycemia?

Insulin Resistance in Nerve Cells Versus Insulin Resistance in Adipose Cells

PK: Yes, I'm not sure where this is going. I know this is a very hot topic in the Alzheimer's field, and a lot of people are studying insulin resistance in nerve cells, and I think insulin resistance in nerve cells is a very different phenomenon than the insulin resistance that we describe in type 2 diabetes. Insulin resistance in type 2 diabetes is mainly driven by skeletal muscle insulin resistance, with contributions from adipose in the liver. Whereas nerve cell insulin resistance I think is a totally different phenomenon and I'm not sure it's connected to them. The other issue is I know that dementia is more common in diabetics, per autopsy. To what extent is this being driven by vascular events, since of course diabetics

have higher risk of stroke and other vascular events compared to non-diabetics. So I'm not really sure where this is going right now in terms of trying to decipher this, in terms of whether it is a "type 3" diabetes or is another of the many manifestations of the diabetes that we already know, and I'm not sure about that.

JB: Let's shift over to a discussion now of the adipocyte, which seems to be central in all discussions recently due to this epidemic of BMI increases that we're seeing in the population. David Ludwig just authored an interesting editorial in the Journal of the American Medical Association talking about is obesity causing disease or does metabolic disturbance due to lifestyle and other environmental/gene connections cause a sequence of events that leads to obesity?[4] So is obesity the cause or the effect of this pandemic that we're seeing of things related to insulin resistance? What's your thought? Maybe it can be an either/or and it doesn't have to be one or the other.

PK: Yes, well our change in lifestyle is clearly driving all this. Our biochemistry—all of our metabolic pathways—evolved over the course of many millions of years. If you look at the DNA—you sequence the DNA—of archeological digs, you know that the human genome has not changed in at least ten or twenty thousand years. So we are the same people, genetically, as our hunter-gatherer ancestors. Our biochemistry evolved at a time when one of the biggest risks to human civilization was starvation, number one. So we're designed to get through the lean times when there is no food and no game. Also we're designed to hunt and to gather. We're not as fast as the deer, but we can outrun the deer; we have more endurance, so we can chase the deer until the deer gets tired and then we eat. We can work in the field day in and day out to gather crops and gather food because if we don't get the food in before the next storm or the next something happens we don't eat.

So we're designed for really quite extraordinary physical activity. But then, of course, what's happened? Then, of course, over a relatively short period of time, our life has become totally sedentary. Now we have to do comparatively very little. And so our biochemistry is still designed to store calories as fat—to store it up for the times when there may not be food, and there are behavioral issues with this: we're prompted to eat, we like certain types of food. It's behavioral, it's metabolic, and we're designed to store fat in all kinds of places, not just our fat cells, but maybe our liver, and our muscle, and other places, just—again—to prepare for the lean times. I think a lot of this really is being driven by the change in lifestyle that occurred very quickly in evolutionary terms, whereas our biochemistry…we're still the hunter-gatherer of our ancestors.

Changing Metabolic Parameters with Gastric Bypass Surgery

JB: Some people call that the thrifty gene hypothesis—I think that Neel first talked about it with the Pima Indians—so let's take that on to an individual who has a morbid obesity situation (a BMI of 40, let's say), they are on multiple medications based on the principles you were talking about earlier, and they go in and they have gastric bypass Roux-en-Y surgery, and voila, within a period of very short post-op, without losing a lot of their extra fat mass, their metabolic parameters normalize. How does that occur?

PK: Well, this has been a subject of considerable discussion and debate. There is one side that claims there is something special about the surgery, and a lot of the focus has been on some of the GI hormones—ghrelin and a number of other GI hormones. It is suggested that these things are altered by the bariatric surgery, and that this has a metabolic effect both on shutting off appetite as well as with

improving glucose, lipids, and other things. The other side of the camp suggests that, well, you've just shut off the spigot of food intake. The person is not eating. Yes, they haven't lost that much weight yet, but just the fact that they are stopping eating actually has a big effect. And so I tend to be a little bit on the stopping-eating side of that fence, although I think that there is truth to both sides.

I used to direct a metabolic weight-loss program where patients paid a lot of money and they would go on a liquid diet where they would all of a sudden go to, say, six or eight hundred calories per day, and you would see the same kind of thing. When patients really stuck to their diets, you would see fasting blood sugars go from 350 down to 120 in literally a couple of days, dramatic changes in lipids, and so you would see this kind of dramatic thing just by stopping the food intake. I think that the rapid improvements that are seen with bariatric surgery, some of this is entirely predictable based on stopping the eating, but I think there probably is something to the story of GI hormones and ghrelin, in particular, that seem to be influenced by the GI surgery. I'm thinking it is probably 75{56bf393340a09bbcd8c5d79756c8cbc94d8742c1127c19152f4230341a67fc36} stopping the food intake and 25{56bf393340a09bbcd8c5d79756c8cbc94d8742c1127c19152f4230341a67fc36} other GI hormones that may be involved.

JB: That's very interesting. I know that there has been some work done not just on ghrelin but things like GLP-1 (glucagon-like peptide-1) and its influence, and of course that then raises the whole things about Byetta and other pharmacological compounds that are used to modulate GLP-1 concentrations, so I think there is this, as you say, probably mixed story that's related to these incretin hormones and how they are influenced by Roux-en-Y surgery, and also the mass of food consumption that's changed by making the alimentary canal so small and getting rid of the stomach, basically.

PK: Right.

Adipocyte Physiology is Now Leading the Field of Bioenergetics

JB: So let's move from there to this emerging story about the adipocyte, which I think is really interesting when we go back and think 30 years ago that if you were an adipocyte physiologist, the last question that people would be interested in knowing is what you did for a living because it was so considered unimportant and maybe even socially unacceptable to call yourself a fat cell physiologist, but now it has moved to head of the class and it is where the action is. So tell us a little bit about this white adipocyte, beige adipocyte, brown adipocyte story. I think it sounds like an amazing new development in the whole field of bioenergetics.

PK: Yes, getting back to our hunter-gatherer ancestors, so one thing our hunter-gatherer ancestors had to do was prevent starvation. Another thing they had to do was to stay warm, and so if you were hunter-gatherer out—especially in a northern climate where it gets cold—that becomes a real issue. Now, all mammals, including humans, have significant amounts of brown adipose tissue at birth. This is particularly apparent in rodents—you can see large amounts of adipose tissue—and the brown adipose tissue is located typically around the neck and between the scapula and in the back. Newborn babies have this, and of course this is an important evolutionary adaptation—when the baby is suckling the baby needs to stay warm, and so you can see why a tissue that is designed to generate heat, to burn lipid, but instead of burning lipid to create energy it is actually burning lipid to create heat, and that's an important evolutionary adaptation and is present in all mammals at birth. But then, what always used to be said is

that with growing up and becoming older, by the time humans were in their teenage or young adult years, the brown adipose tissue was gone.

Well, with the advent of PET scanning, and PET scanning is typically done to locate tumors, they started noticing the PET scanning was picking up brown adipose tissue in humans. There have been many studies documenting the presence small depots of brown fat in humans. Now, how important is that brown fat in humans? It is fairly metabolically active, but is this really burning a lot of calories? Can we capitalize on this? So these brown adipose tissue depots are typically located in the back and the neck, but if you take a mouse, for example, and you put a mouse in the refrigerator for a while and you chill it down, the mouse will not only activate its brown fat, but it will also take his white fat and make it brown-like (more brown), and that's been called a browning process or actually it is now even called beige fat, because the white fat never becomes as brown as the brown fat, but it does darken.

And this darkening is because it accumulates mitochondria. As it accumulates mitochondria it is burning lipid, it uncouples oxidative phosphorylation, and it starts to generate heat. So in a mouse, it has been well-documented that his white fat can adapt the same way. I think it is very possible that humans have the ability to do this as well—that we have the ability to also make our white fat a little bit beige in response to cold. Now of course as humans we don't chill ourselves out as much. We wear clothes. We have thermostats. We heat our houses. And so I think it's a little bit trickier to demonstrate this in a human, and humans naturally use our brain to manipulate our environment so that we don't have to be exposed to cold as much as a mouse that is living in a hole in the ground somewhere. But I think this process in humans probably parallels that in a mouse, probably not as robust, but still it's probably not totally absent.

JB: When I look at this story, I'm reminded that these mitochondria that are being activated—a kind of biogenesis of mitochondria—that the mitochondria have all these cytochromes in them and those cytochromes, which are the energy shuttle system for these electrons that are involved with energy production, all contain the trace mineral iron. So iron is the origin of the chromophore that ultimately turns these tissues brown, stains these tissues brown. So what we're really doing is inducing, then, gene expression, it would appear, of the energy processing centers, which I guess the emerging view is that mitochondrial inactivity is associated with poor bioenergetics and diabetes and mitochondrial activity, as you get with exercise for instance, is associated with improved bioenergetics and improved insulin sensitivity and increased glucose utilization and lowered diabetes. Is that how this model is all kind of fitting together?

PK: Yes, the mitochondria is very important in different tissues and in different ways. A minute ago we were talking about the mitochondria in the fat cell and its role there might be to burn lipid and to generate heat in this beiging or browning process. Now muscle, of course, uses a lot of glucose, and in fact when you are measuring insulin sensitivity in humans usually you're talking about muscle as the main organs of this. Muscle mitochondrial function is also critical for not only the burning of lipid, but also the improvement of the whole glucose uptake process in skeletal muscle, and so many studies have been done trying to look at muscle gene expression and muscle function in humans, and it is very strongly correlated with insulin sensitivity: the better the mitochondrial function, the more insulin sensitivity.

JB: So that leads to a clinical question that I'm sure our listeners are thinking about, and that is, "Okay, how does a patient beige their white fat?"

Can You Convert White Fat to Beige?

PK: I don't know. Could we develop a drug that could do this? Should we just get out more? Well, there are lots of reasons we should get out more. Perhaps we should not just go to the gym and exercise in a controlled temperature environment. Maybe we should get outside and expose ourselves to the elements more. Usually I tell my patients to exercise, and I don't care how you do it, just find a way to exercise. If you hate going outside, then go to the gym by all means, because any way you get it done. But I think maybe the exposure to colder weather probably does stimulate something.

JB: Yes, I think that the interesting combination, as you're saying, between exercise, which does have a noradrenalin effect obviously on activating brown fat, and also doing it in a cooler place, might be an additive effect. There are some studies that I have seen in animals where they have shown that synergy in improving energy economy. Let me move to an area that I know you have considerable experience in. I have seen some extraordinary work that you have done and published in humans related to omega-3 fatty acids and its relationship to insulin signaling and lipids and inflammation.[5],[6] Tell us a little bit about this emerging story because it seems like that's a very controversial topic at the moment, the whole omega-3 fat story.

Examining the Effect of Omega-3 Fatty Acid Intake on Adipose Tissue

PK: Right. There have been studies on omega-3s and fish oils for many decades now, and it's very clear that omega-3 fatty acids lower plasma triglycerides, and there are fish oil preparations that are pharmaceutical grade on the market now that do this and are indicated for this. Omega-3 fatty acids also have a slight effect to decrease platelet aggregation, and this might be important in coronary prevention. To be clear, omega-3s are not as potent as an aspirin, but again, in population studies, when you look at omega-3 intake, you often find that omega-3 intake is correlated with a lot of benefits, including coronary prevention, and this might be one mechanism.

Omega-3s also have an anti-arrhythmic effect on the heart, probably through membrane stabilization in preventing of arrhythmias in the heart. Another interesting thing about omega-3s is that they are anti-inflammatory. There have been many, many studies that have looked at the anti-inflammatory effects of omega-3s for rheumatoid arthritis, or inflammatory bowel disease, or asthma, and for other chronic inflammatory diseases. And there is variable benefit. I think probably for rheumatoid arthritis there is a clear-cut benefit of omega-3s. Now, it's not as potent as anti-TNF antibodies and other types of treatments, but certainly omega-3s do have a role.

So we wondered whether omega-3s have an anti-inflammatory effect that would be useful in patients with metabolic syndrome, so we did a study where we recruited patients who were not diabetic, but they were pre-diabetic. Most of them had impaired glucose tolerance and they had multiple features of metabolic syndrome, and we randomized them to 4 grams a days of omega-3 fatty acids or placebo.

What we found is that there was a decrease in the number of macrophages in their adipose tissue. We found some other signals that were beneficial signals, such as decrease in certain cytokines and an improvement in adipose tissue capillarization. If there is better blood flow to the adipose tissue then probably there would be less dysfunction. However when we looked at insulin sensitivity, we did not find an improvement in insulin sensitivity. So we saw some benefits on reduced inflammation, but not an

improvement in insulin sensitivity.

Maybe we just need to give more omega-3s or we just give them for a longer period of time. I mean let's face it, some drugs are just TZDs, which are relatively slow-acting and it takes at least three months even to see an effect, so maybe omega-3s need to be given for a longer period of time. So I'm interested in further pursuing the possible role of omega-3 fatty acids in metabolic syndrome, in particular, as an adjunctive treatment. And we certainly recommend a drug right now for treatment of hypertriglyceridemia, and as even if there is a suggestion of coronary prevention (there may be a coronary preventive effect).

JB: Dr. Kern, as you look out at this landscape, you've got this portfolio of drugs that are now available for the management of type 2 diabetes, and we see a rising tide of insulin resistance, and there are a huge number of not-properly-diagnosed diabetics and certainly even a greater number of pre-diabetics. So what would you, from your crystal ball, see as the future for managing this epidemic? Where are we going to go? We can't build renal dialysis centers fast enough. We don't have enough endocrinologists. There must be some solutions on the horizon. Where do you think they reside?

PK: Well, the Holy Grail will be a good obesity drug, certainly, because obesity is driving the whole process. There are a small number of obesity drugs on the market right now. They are not the greatest in terms of effectiveness versus side effects. I tell my patients right now: ten pounds of weight loss is far more effective than any drug I could possibly give you. So I push this with patients very strongly. But of course, we live in a free society, and so we can't stop the TV commercials. We can't stop the restaurants from offering food that we really, really like to eat, and so there are lots of pressures.

I think one solution to this would be an equivalent of a statin. I mean, look at what the statins have done for lipid management. Anybody can manage lipids now; in 90{56bf393340a09bbcd8c5d79756c8cbc94d8742c1127c19152f4230341a67fc36} of the patients all you do is write a prescription for a statin. Whereas there was a time, which I remember, before statins, when you were struggling with trying to use cholestyramine and niacin and other drugs which were just not terribly effective and very cumbersome. So I think we're still in the niacin/cholestyramime stage in terms of treating obesity. We're using drugs that are just not terribly good, and we need a statin-equivalent. If we could come up with that, that would be the single best thing.

Now, in addition, to the extent we could find drugs that target the problem, and if the primary problem is insulin resistance, then we'd like to have better insulin sensitizers. In many ways, the TZDs, like pioglitazone that is still on the market, was a great drug in terms of improving insulin sensitivity, improving lipids, even a slight anti-hypertensive effect, but unfortunately it is caught up in a morass of post-hoc analyses and lawsuits. There are some side effects which are of concern. Unfortunately TZDs and the PPAR gamma agonists, at least the PPAR gamma agonists that are out there right now are not the answer, but I think if we could find better insulin sensitizers that don't have the same off-target effects, I think that will also be a very important treatment.

JB: So that then raises a question that you were addressing earlier about lifestyle intervention, exercise, diet, nutrition, food supply, all these various complex questions. In your experience, having run large clinics and individual patient management, what do you think the receptivity is, or is it changing it all, as it relates to people starting to take charge of some of these variables that send the signals that encourage

obesity and insulin resistance?

The Behavioral Side of Obesity Management

PK: Well, there are many people out there who are taking charge of their lifestyle and doing a really good job. But unfortunately there is a large mass of people who really don't have the insight or the ability to manage things terribly well. So, yes, on the West Coast, in California, you have people, who, whether it's cosmetic reasons, health reasons, or whatever, will go out jogging on the beach every day and take really good care of themselves and eat tofu and bean sprouts, but unfortunately in many other areas of the country, such us Appalachia in Kentucky, that doesn't happen. And in fact there are many cultural things that have been done over the years that work against us.

If you look at a couple of generations ago, if you look at just life back in the 1920s and 30s, people had to walk a lot. You walked into a building, and you had to climb the stairs to get up a few flights. You would take walks in your neighborhood. You didn't have convenience foods that you pop in the microwave. So you actually had to work a little harder just to eat. And now there are so many things that are working against us. If there is a stairway in a lot of your buildings, it's a fire stairway in the back someplace where you don't even know how to get into and it takes you outside, so people don't use the stairway. People don't get out and walk. Food is way too easy. Everywhere you go there is food in front of you. You go into some office somewhere and the secretary has a bowl of M&Ms on her front desk right as you walk in. Why is that there? There are so many things that work against us now, lifestyle-wise, that it becomes very hard.

JB: And do you think that maybe part of this, and I've heard the term sociogenomics, that there is a social structure that is one of the major parts of this difficulty, that we lack the peer reinforcement, we lack appropriate messaging, we lack finding how to do this in a fun way with people that would develop a social support system rather than insulated, isolated patients who are fighting against disease and have this fear model of how am I going to survive against the onslaught of a serious disease rather than having a peer support group. Do you think there are social structural changes that can be implemented within the context of medicine, or do you think that's a bigger problem outside the purview of medicine?

PK: The people who focus on behavioral management of obesity…I mean, there are many people who work very hard on the behavioral side of obesity management, and one of the fundamental principles to try to change your social structure: get the food out of your house; if you want to lose weight, get your husband to lose weight with you because you don't want your husband to sit around eating donuts while you're trying to diet; don't go to that buffet; bring your own bag lunch with you. There are many different things to try to address the social situation, and some people are successful at doing that. But we live in this toxic environment and it is very hard for people to keep this up. It's not impossible, but it's very hard since food is everywhere. And there is a huge economic driver to this. Food is relatively cheap. We produce a lot of food, and usually the worst food, of course, is the cheapest food. And people want to please you, so you go someplace and someone throws food at you as a way of making you happy and pleasing you. It's a social thing. You go over to someone's house, you bring a casserole. You bring food with you. It's built into our social structure, but of course some of that social structure is back in the Depression days when we brought food because people were hungry. We're not hungry anymore. I think some people are very good at navigating the social structure, but it's all around us and it's very hard to navigate it forever.

JB: It would seem to me from what you were talking about earlier that this emerging understanding of beiging of fat and activating thermogenesis and even bringing into it some of the things that we've learned from the metabolic effects of Roux-en-Y gastric bypass surgery and how that influences incretin hormones and regulates blood sugar control, it seems that these may be some frontier discoveries that are really going to change the landscape, both from a nutrition and lifestyle intervention perspective, but also from a pharmacological perspective. So there may be some bright lights here that is not a train coming from the other direction, it is maybe bright lights at the end of the tunnel. At least I would hope from what you've described that we've got some options that we didn't have, here, five years ago.

PK: Yes, I certainly hope so.

JB: Well, I want to thank you very much. I think this has been an extraordinarily good clinical news-to-use overview of both the nature of the problem and some of the things that can be done and where the future might take us. Your work is really seminal. I think the work that you've done on adipocyte physiology and looking at the interaction between the immune system and adipocyte physiological function and how that connects to insulin resistance, this—to me—is where the action point is in the future of getting grips and a handle on what really what is a pandemic—it's a global pandemic. So keep up the great work and thanks so much for sharing this information with us.

PK: Okay, thank you very much. It's been a pleasure to be here

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