

December 2014 Issue | C. Ronald Kahn, MD

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Welcome to Functional Medicine Update, December 2014, the third of a three-part series on diabetes. As you recall in the first of this three-part series we had the pleasure of interviewing Dr. Philip Kern from the Barnstable Diabetes and Obesity Center from the University of Kentucky School of Medicine who really laid the groundwork for understanding—in the field of clinical endocrinology—what is type 2 diabetes? What is the nature of its problem in our society today? How does it relate to obesity, and what are the kinds of things that a clinician should be aware of as they diagnose, assess, and ultimately develop a treatment program for their patients?

In the second of this three-part series we had the privilege of interviewing Dr. Osama Hamdy from the Joslin Diabetes Center at Harvard Medical School who did an extraordinary job in helping us to understand how lifestyle intervention could play a very important role in modulating type 2 diabetes both in the early stages and then in the sequelae of events of more severe consequences. In this particular discussion he helped us to understand how important personalization of the program might be, and also the important role that medical nutrition therapy might have in helping to accelerate the benefit in patient management and make compliance and adherence more successful.

In the third of this three-part series we are going to be very fortunate to hear from arguably one of the world's—if not the world's—leader in insulin signaling, Dr. C. Ronald Kahn, the director of the Joslin Center, who will really help us to understand what the 21st century view of this disease is (its etiology), and how it presents in multiple forms based upon different types of disturbances and the understanding of how genes are translated into the phenotype.

So without further ado, let's move to our discussion with Dr. C. Ronald Kahn.

INTERVIEW TRANSCRIPT

Clinician/Researcher of the Month

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Well, you know how excited I am each time we have this opportunity to share with a world-renowned clinician/researcher and of course this month we are, I would say, at the top of our game. We have the opportunity to be speaking with Dr. C. Ronald Kahn. I think the name alone, for those of you in the field of diabetology or metabolic diseases, already know much about what I'm going to say. He is a world-recognized expert, obviously, in diabetes and obesity research, and a preeminent investigator in the area of insulin signal transduction. As to his professional background, presently he's a senior investigator, head of the section on integrative physiology and metabolism at the Joslin Diabetes Center and the Mary K. Iaccoca Professor of Medicine at Harvard Medical School. He served as the research director at Joslin from 1981 to 2000 and served as the president of Joslin from 2001 to 2007. He is currently the center's Chief Academic Officer. I could spend the whole of our time just talking about Dr. Kahn's achievements. I was first introduced to his work when I started to recognize that the emergent understanding of diabetes was really tied to the personality of the insulin receptor and its insulin stimulated receptor, tyrosine kinase, which was really Dr. Kahn's discovery.

The Kahn Lab is focused on understanding how the event—this tyrosine kinase activation within the insulin receptor and insulin receptor substrate—activates the complex signaling network that leads to the multiple actions of insulin. And his group, over the years, has showed that following activations, several insulin receptors substrates become tyrosine phosphorylated, so this whole kinase intracellular signal transduction process is mediating this process and, as intracellular messengers, they then talk to other intracellular signaling proteins and we get into this very complex nature of how genes are ultimately signaled and how we alter glucose transport and see the manifestations across the pleiotrophy of what we call type 2 diabetes.

I think we would have to say over the 660-plus publications of Dr. Kahn's career, that he has been the pioneer in really helping to understand, at the molecular cellular biology level, what is type 2 diabetes? We use that as just an introduction to the vast panorama of work that you've been involved with, Dr. Kahn. I guess I would just ask, how did you get started down this road, being a pioneer? You know, it's always one of those remarkable things—that some “ah-ha” must have occurred on your path that led you into these extraordinary discoveries.

Major Discoveries About Insulin Took Place in the 1970s

CRK: Well, my own experience really began as a fellow at NIH. I was with Jesse Roth and Phil Gorden, who back then were really leading the charge on trying to understand the new frontiers of hormone action. It's hard to believe that really only 40 years ago we really had no understanding of how insulin worked at the cellular level. There were theories that insulin might get into the cell, and interact with enzymes in the cell, that it might covalently attach to these enzymes or to cell proteins through disulfide bonds (because insulin has disulfide bonds), and many other theories. But going back now to the early 1970s, there were a series of discoveries in several laboratories, but particularly in the laboratory of Jesse Roth, that really began to say that insulin and other peptide hormones were acting through membrane

receptors in a way that would allow the hormone to signal the cell from the outside and create an intracellular signal. And there were many other discoveries that also supported this kind of view; certainly this was not alone. So initially we got started looking at the insulin receptor mainly as an insulin binding protein, that we could show that it bound insulin in a way that was consistent with biological activation rather than like an antibody binds insulin, but not in a way that is related to its biological activity but the receptor binds related to its biological activity. And then we were able to do many studies that got us into beginning to understand the structure and after about really almost a decade from the time we did the first insulin-binding experiments, we came to realize that the receptor was the tyrosine kinase. There had been one previous example of the tyrosine kinase receptor, which was the EGF receptor, and nobody really knew that the insulin receptor would be like that because it has very different structure from the EGF receptor. But we thought, well, since we had this new potential mechanism, let's try. And Misako Kasuga, and Anders Karlsson, and I set out on a series of experiments that initially were a little bit disappointing, but we stuck with it for a while and sure enough after several months we were really able to see that this receptor had tyrosine kinase activity, and that changed the whole paradigm of insulin action.[1]

JB: When I think back to my own training in medical school in the late sixties, I am reminded that we had very little discussion at that point about the different voices of insulin and the fact that there could be this form of diabetes that was associated with hyperinsulinemia as a consequence of blunting it with an insulin signaling mechanism. It must have been quite a remarkable shifting paradigm within the field of diabetology when you made these discoveries and started to really explicate how these signals could be both created and could be inhibited.

The Insulin Receptor and Its Substrates Control Insulin Response

CRK: You're right, Jeff. I'm pretty much contemporary with you in when I did my medical training and basically I think that most people thought of diabetes as really insulin deficiency, although we knew that there were type 2 diabetics who were insulin resistant, but the question of how that resistance occurred was completely mysterious. There were some studies that suggested that maybe these people had increased insulin degradation, or perhaps they had insulin binding proteins in the blood (not antibodies, but other proteins that interacted with insulin in the blood), and that these substances might somehow create insulin resistance. But once we got the receptor, and once we knew that the receptor was there, we showed that the receptor itself is regulated. Just like insulin levels can go up and down, the receptor levels can go up and down, and of course if you have more insulin you get more insulin action; if you have less insulin you get less insulin action. But likewise, if you have more receptor you get more insulin action, and if you have less receptor you get less insulin action. And that's true through every step in the process, so the substrates of the receptor and the intracellular signaling enzymes and transcription factors which relate to the receptor all can become factors in controlling the insulin response. In fact, you could think that there are really many more controls on insulin action/insulin signaling than there really are on the controls of insulin secretion because of all of the different steps that are involved in this process, and of course all of the different tissues that are responding, which can have not only some differences in the exact signaling cascade, but can certainly also have differences in how they develop insulin resistance.

Kinase Intracellular Signaling: A Metabolic Relay Race

JB: You know, one of the things that I think you can help us with probably better than anyone I know is

to assist our listeners, which are principally clinicians, to understand a little bit more about this kinase intracellular signaling transduction process, which is a little bit like a molecular relay race with some degree of feedback control. Could you help us understand...I know it's a very complex network...but maybe you could help—for the clinician—to understand what goes on inside the cell relative to this complex kinase array.

CRK: Sure. This is really somewhat complex but I think it's pretty simple if you think of it this way. The receptors for insulin and other peptide hormones and neurotransmitters sit at the surface of the cell, and their job is to recognize their hormones or ligands, whether they be insulin or growth hormone or other peptide hormones or catecholamines, to recognize those hormones by binding them with a high affinity and a high specificity. Once they bind, the hormone doesn't really ever enter the cell for signaling purposes. It may enter the cell eventually to be degraded, but it doesn't enter it for signaling purposes. What it does is it triggers a change in shape of that receptor (a change in conformation). In the case of the insulin receptor, this activates an enzyme activity that is on the intracellular part of the receptor, and that is tyrosine kinase activity. And what the words "tyrosine kinase" mean is it's just an enzyme that can put a phosphate group onto tyrosine residues of proteins. And the insulin receptor puts phosphates on tyrosines, both on the insulin receptor itself and on intracellular proteins that are its substrates. These are called insulin receptor substrates 1, 2, 3, and 4. So these substrates then have this little extra addition to certain tyrosine residues. And they become the intracellular messengers of insulin action. They do that because now other proteins in the cell can bind to the sequences around these phosphotyrosines in a way that allows them to become activated, and so it is kind of a relay race. I think your analogy with a relay race is a very good one. The receptor is kind of the first person in the relay. The receptor hands the baton—in this case a phosphate group—off to the substrate, IRS-1 or IRS-2. And then the substrate actually in this case doesn't pass the phosphate group (it doesn't pass the baton), but what it does is another protein in the cell, maybe an enzyme—like there's an enzyme called PI3 kinase that's an enzyme that is involved in insulin signal transduction—and it binds to this tyrosine phosphate group, and it gets activated, and then it carries on the chain. So it is kind of a relay race. In some steps a signal branches out, so you can have two or three different directions it goes. In some steps there is regulation. And so this allows the whole signaling of insulin at the cellular level to be finely tuned so that each cell type can respond in the way that is most appropriate for it.

JB: So as we go down that pathway—as you go through PI3 kinase and down into Burton's tyrosine kinase and into SYK and ultimately through GSK-3—there is a confluence of that network of that pathway with the inflammatory pathway, which is interesting from a physiological perspective and may account for some of the things that you see clinically with patients that have inflammatory crisis, say, in the ICU and they end up with hyperglycemia. So how do those networks interrelate—the inflammatory pathway and the insulin signaling pathway?

CRK: Right, so there are many hormones and growth factors that use some of the same similar components for signaling. There are a number of tyrosine kinases; they have different substrates. Many hormones and many growth factors activate this PI3 kinase pathway that I was talking about, and some of the downstream pathways that you mentioned, including AKT and others. I like to call these the critical nodes of insulin signaling. Because these are the parts that not only insulin acts on, but other hormones may act on them in similar ways, or in ways that inhibit the action of insulin. So you mentioned, for example, inflammatory cytokines. We know that in states of inflammation, there is insulin resistance. In fact, this is, in part, what goes on in the insulin resistance when people have infection: inflammatory

cytokines go up, those inflammatory cytokines create resistance to insulin action at the tissue level. And so in a normal person we can compensate by making more insulin, but of course a person with diabetes may not be able to compensate and their diabetes may go out of control. So the way that works is that these inflammatory cytokines also activate a signaling network and some of the steps are similar, but there are also some that are different. For example, when these inflammatory cascades get activated, there is a group of kinases—those are intracellular enzymes that can phosphorylate (put phosphate groups onto protein)—that can modify serine residues of IRS proteins. Now I told you that the insulin receptor modifies tyrosine residues, and that has a positive insulin action. When these inflammatory cytokines are activating their system, they cause serine phosphorylation—a different amino acid in a different place in the chain—and that's a negative signal. So we've got tyrosine phosphorylation as a positive signal, and serine phosphorylation as a negative signal, and it's kind of a balance of how these things will play out in any given individual.

JB: So if we had a patient—trying to take this from the bench to the bedside a little bit, in this discussion—who had, say, a chronic inflammatory state as a consequence of, say, activation with lipopolysaccharide from gram negative bacterial cell wall debris, and so they had an activation of the toll-like receptors that activated their inflammatory pathway. It seems there could be cross-talk, then, with their insulin signaling to precipitate these serine phosphorylation events, which then could blunt insulin sensitivity. Is that a reality?

Inflammation—Major and Minor—Can Influence Insulin Signaling

CRK: Yes, that's actually correct. And there is a lot of evidence for that. In fact, there's also evidence that not only in states of major inflammation—like you were talking about: infection, and bacterial infection, and so forth—but these can be chronic inflammatory states of a mild degree, like associated with obesity. Obesity is associated with inflammation. There's actually inflammation in adipose tissue in obesity, and those inflammatory cells and the inflammatory cytokines that are produced can do the same thing; they are creating insulin resistance at the cellular level, interfering with these downstream steps and insulin action, and when that occurs, that will lead to insulin resistance.

JB: So let's take it one step farther a little bit as we head on towards the promoter regions of genes inside the nucleus. So we have these so-called orphan nuclear receptors, which are agents that are kind of communicating the message from the kinase signaling pathway ultimately into the specific regions of the genes where the genes are going to be expressed. The one that obviously comes up often in type 2 diabetes and ultimately adipocyte physiology is peroxisome proliferated activated receptor gamma or alpha. Tell us a little bit about how these nuclear orphan receptors play a role in this process.

CRK: Yes. Well, I'm going to back you up one step. First let's do the normal part and then we'll do the sort of cross-talk part because I think you're going right already to the cross-talk and I'm going to finish up first the normal part. So the normal part is that the enzymes that are activated by insulin—PI3 kinase that activates this downstream enzyme called AKT—what they actually do is act on transcription factors, and the most common or important one that they act on is a transcription factor called FOXO1. This transcription factor normally sits in the nucleus of the cell, and what it does is it turns on genes that make enzymes for gluconeogenesis. That is, enzymes that are going to make more glucose in the liver. So when FOXO1 is in the nucleus, which it is in the liver normally (in the nucleus), it's telling the liver cell: make more glucose. And that of course will bring the blood sugar up. What insulin does is through its cascade it

causes phosphorylation on a serine residue of FOXO1, and that actually keeps FOXO1 out of the nucleus and keeps it in the cytoplasm of the cell, and that's where it's inactive, so that brings down the level of gluconeogenesis (glucose production by the liver). So that would be the normal example of how insulin regulates gene expression.

Now, as you were pointing out, at this level there is also a lot of cross-talk. There is cross-talk between other factors that can regulate FOXO1, for example, directly, but also other transcription factors and even nuclear receptors, both some which have known ligands and some which have unknown ligands. Nuclear receptors are really the other big class. I said the insulin receptor is a membrane receptor, so peptide hormones and neurotransmitters use membrane receptors, as do certain other chemical substances like taste receptors and other sensory receptors, and then the other big class of receptors are nuclear receptors, and of course that includes the receptors for steroid hormones, thyroid hormones, and also receptors for a lot of small molecules. PPAR gamma is a nuclear receptor that is thought maybe normally to bind some lipid molecules, but nobody really knows for sure which lipid is the most important for PPAR-gamma, so it's sort of been considered not a true orphan receptor, but it's somewhere between a defined receptor (a normal binder) or not, but we do know that certain drugs, like the thiazolidinediones (pioglitazone, troglitazone, rosiglitazone, all of this class of drugs) bind to PPAR-gamma. PPAR-gamma is mainly in fat cells, and in those fat cells it turns off that inflammatory response that is going on in adipose tissue and it actually allows the insulin resistance to improve.

Insulin Events Are Cell Specific

JB: So when we look at this whole extraordinary symphony, and we've only probably talked about a few instruments in the orchestra—there're are lots of other ones we haven't talked about, I know, or probably many that we are yet to even discover and understand—and you then put the additional complicating factor that these events are occurring in cell-specific ways, so there might be a difference in how these are orchestrated in the macrophage versus the adipocyte versus the cardiomyocyte versus the beta cell of the endocrine pancreas. Are there some general principles that we take away or is there a cellular voice that is stronger like the adipocyte or the hepatocyte that helps orchestrate this process?

The Four Most Important Tissues in Insulin Signaling

CRK: Well, this is a bit of a tricky question because many different tissues play a role. In terms of insulin signaling, the four most important tissues in terms of insulin signaling are the liver, where insulin turns off glucose production; the fat cell, where insulin helps the fat cells store the bits and pick up glucose; the beta cell (the insulin secreting beta cell), because actually insulin action in the beta cell helps the beta cell have normal glucose sensing, and you know that one of the defects in type 2 diabetes is the beta cell doesn't respond normally to glucose, that's why you get relative insulin deficiency. The beta cells are there, but they are just not functioning very well, and that's—we believe—also part of the insulin resistance problem. And then of course the newest frontier of insulin action is the brain. Traditionally both the beta cell and the brain were not thought of as insulin sensitive tissues, but in fact both of them are insulin sensitive tissues. Not a lot of insulin gets across the blood-brain barrier but some does, and in particular around the hypothalamus, the important part of the brain for control of metabolic functions, it's a very key spot for some insulin action, so that insulin resistance in the brain can also be quite a contributor to the overall problem in type 2 diabetes or metabolic syndrome.

JB: Does this tie at all to what I've read in the literature as euphemistically termed "type 3" diabetes?

Thoughts on Insulin Resistance and Alzheimer's Disease

CRK: Well, I think that what the connection is with the brain that people are thinking of as type 3 diabetes is also that there is some evidence—we've actually shown this in our own laboratories but others have shown it as well—that insulin resistance at the brain, or at least a lack of insulin action at the brain, may cause changes that could contribute to neurodegeneration, and potentially contribute (at least in a collaborative way with other factors) to the pathogenesis of Alzheimer's disease. So that some people have now actually written articles and have given lectures titled "Is Alzheimer's Disease Type 3 Diabetes?" It's a little bit of a stretch to say that it is "type 3" diabetes because Alzheimer's disease really isn't diabetes at all in the sense of blood glucose control, but what we're trying to say is that maybe insulin action of the brain really does have some protective roles in brain function, also IGF-1 (insulin-like growth factor 1) action at the brain. And so one of the great, new, exciting research areas just developed in the last two or three years has been to actually do some very small clinical trials looking at the potential for giving insulin (potentially intranasal insulin, which might get to the brain at a little higher concentration) and see if that would change the course in some way of Alzheimer's disease.[2],[3] We don't think that this is the primary problem, so it's not going to necessarily stop it or prevent it completely, but if you could slow the progress, that would be great.

JB: Let me, if I can, go back with you for a second. I know of your many publications, one that you were principal author on in 2014 related to cell surface markers in the different types of adipocytes.[4] I recall in my cell physiology studies way back when, we didn't really think about types of adipocytes. Now we're talking about both white and brown and these beige adipocytes. Could you tell us a little bit about how that fits into the story and the work that you are doing?

Research is Looking at Brown Fat to Burn Energy and Control Weight

CRK: Well, this is actually another story that has evolved rather dramatically over the last five-to-ten years. I think all of us (all clinicians—MDs) know about white fat. That's the fat that is spread throughout the body, under the skin, inside the abdomen, around blood vessels, around the omentum and so forth. All of these fat cells, which are either white or yellowish in color are referred to as white fat, and they are fat that is specialized for storing triglyceride. And of course their special function is to store that fat from energy we're taking in now so that if at some time in the future we don't have access to food, we have energy stores to help live on. Now, most of us, even the leanest out of us—I mean even people who have BMIs down at 20 or 21—have still a few kilograms (sometimes several kilograms) of white fat. But there is a second kind of fat that has been known to exist for quite a long time, but people thought wasn't so important in adult humans and that's called brown fat. And brown fat is different from white fat in many ways.

First of all, as the name implies, it has a brownish color. That's because the fat is loaded with mitochondria, and mitochondria have a lot of enzymes that are iron-containing enzymes, so it gives the fat a brownish color. In mice and in rodents, this brown fat is collected into a single collection that is located on the back, between the shoulder blades (the interscapular region). In newborn humans, there is also interscapular brown fat, but what we found about six or seven years ago using PET imaging is that in adult humans most of the brown fat is scattered in little collections in the neck and the anterior part of the

neck: the anterior cervical area, the supraclavicular fossa, down the axilla, and down in paravertebral areas, going through the thorax and even down to the pararenal areas in the retroperitoneal space. And this brown fat, spread out through all these areas, is really not a big organ. It's not like you can go in there and simply cut out all the brown fat because it is kind of mixed in with the white fat, and we believe that whereas most people have kilograms of white fat, probably the average human has somewhere around 50 or 70 grams (not kilograms—50 or 70 grams) of brown fat, but this is very important, because this brown fat can burn energy. A hundred grams of brown fat can burn 350 calories a day if it is fully stimulated, and that's a pretty good amount of energy. It does it and it generates heat, so a lot of interest now is can we convert white fat to brown fat or have people give drugs that will make more brown fat that might help then either lose weight or at least keep weight off that they're losing by other means?

And then, as you mention, there's this new third kind of fat, which is called beige. And as the name implies, it is somewhere between white and brown. And what happens that defines beige fat is that in both experimental animals and in humans. If you put people in the cold chronically, you stimulate brown fat or beige fat to make more energy (burn more calories to keep you warm), and when they do that, some of the fat cells that are mixed in the white fat will start to show up as these kind of beige fat cells. So, what's important about all this in terms of insulin is that the more white fat you have, the more insulin resistant you're going to be, particularly if it is intra-abdominal visceral fat. On the other hand, the more brown fat—or perhaps brown and beige fat—you have, the more likely you're to be lean, be able to burn calories, even without exercise (this is thermogenic calories), therefore you'll also be leaner, less insulin resistant, and because the brown fat uses a lot of energy, the good news is that also helps you keep your weight down and your glucose down.

JB: So as we look at the emerging story around beige fat—things like cold and other factors that may be beige fat-inducers—is there some hope that lifestyle modification might actually be a component that could activate beigeing of fat?

CRK: Yes, I think that what people are looking at mainly is the possibility of developing drugs that could promote more beigeing of fat, but at least in experimental animals we can show that you can also activate beige and brown fat by putting them in a cooler environment, and you can do that in humans over the short term. You can put them in a cooler environment. It doesn't have to be all that cold. It has to be 60 or 62 degrees Fahrenheit, and as long as people are not dressed warmly—as long as they are dressed in light clothing—we usually, for these experiments have people dressed in a hospital scrub suit—so if you're in a hospital scrub suit in a 60 or 62 degree room, that is enough to activate your brown fat, and if you did it chronically it would probably make some beigeing of fat, and this would probably help with energy expenditure, but of course if you still eat a lot, that isn't going to be able to overcome eating everything, so one would want to do this along with trying to lose weight through other means.

JB: Two quick additional questions, one of which is this emerging belief that the gut microbiome plays some role in modulating this whole glucose control/insulin control process. What's your thinking about the emergence of this concept?

What Role Does the Gut Microbiome Have in Modulating Insulin Control?

CRK: Yes, this is an exciting new area of research. We're actually doing some work in this area ourselves. The gut microbiome refers to all the bacteria that are in the gut. These bacteria are not only

living in our gut, they are helping us metabolize food, they are making various bacterial products which can affect our metabolism, and they are also doing other metabolic processes like helping us metabolize bile acids to make different bile acids. So the gut microbiome can be a big contributor to overall metabolism and health. The gut microbiome has been certainly linked with weight gain. Different microbiota seem to promote more weight gain and others seem to protect less weight gain, and that's certainly one aspect. What we're trying to find out now is are there also microbiota that can promote more insulin sensitivity and others that would promote less insulin sensitivity for example, because not everybody who is overweight is insulin resistant as the next person and maybe that's also a factor of the microbiome. But this is really a new area and I think we have yet a lot to learn there.

JB: I have also been following the literature of David Jacobs and Duk Hee Lee that seems to be getting some degree of interest in the field at large that there is an association between accumulation of persistent organic pollutants and insulin resistance or altered insulin signaling.[5] Does that seem to be tracking in a way that has any support?

The Environment: "The Last Frontier of Medical Research"

CRK: Well, what I would say is that I sometimes call the environment the last frontier of medical research, and what I mean by that is, you know, nowadays we have terrific tools to investigate genetics. We can sequence your genome or my genome and we can know every base on every chromosome from the beginning to the end, virtually, if we wanted it, right? So we have the tools to know in-depth genetics and we have tools to know in-depth how those genes are expressed by gene expression analysis, and how those expressed genes make proteins by proteomics, and how those protein functions by metabolomics. But I think that the great unknown factors in common diseases like diabetes, metabolic syndrome, obesity, and even cardiovascular disease are other environmental factors. You know, we focus right now on the obvious things: how much we eat, how much fat is in the diet or how much simple sugars are in the diet, fructose or other things, but we really don't have a good handle on all the environmental factors. They could be airborne environmental factors, like air pollutants. They could be other things that are taken in by mouth which are non-nutritive, including both contaminants and natural contents of foods and other foodstuff. And of course they could be other kinds of organisms. We talked about the gut microbiome, but it could be, of course, other microbiota too. So all of these things I think are really going to be important modifiers of genetic risk for diabetes, obesity, insulin resistance, and so forth, and I think one of the hopes that I have for the future but I think we're still a long ways from this is to really have the same kind of research tools to study the environmental factors that we do to study the genetic and other molecular factors that we look at.

JB: So I don't want to put words in your mouth and this is probably a little bit of a leading question. Given what you just said, which has kind of an epigenetic ring to it, do you think that the concept of healthcare lifestyle medicine will have a role to play in the combatting of this rising tide of type 2 diabetes as we move forward?

CRK: There's no doubt that lifestyle modification even of the factors we already know can make a difference. This has been shown by the Diabetes Prevention Program, Da Qing Study in China, by the Helsinki study, by many—studies show that the lifestyle interventions (just doing the things we know: exercise, lower calorie diet) can make a difference. I think that what we don't know yet is what will be the lifestyle modifications of the future and how will we effect those, because, for example, if we want to

affect the microbiome in a certain way, will people need to take probiotics or prebiotics to do that, or if we want to affect some other factors like different pollutants, or different environmental toxins that might modify our system, how would we change lifestyle to modify those? But I do think that a lot of these things will be lifestyle variables, some of which will be easier to control than others.

JB: Well Dr. Kahn, on behalf of the listeners and clinicians around the world that will have the privilege of listening to you, I want to thank you for both the extraordinary breadth of things that you were willing to talk about and how very clear your responses were and really news-to-use in condensing down all the years of your contributions and more than 660 publications is not an easy thing to do, but I think you did a very, very good job of it. We thank you very much and I think this will positively affect literally thousands of clinicians and hopefully therefore hundreds of thousands of patients as they listen to this message, so thank you for the time spent with us.

CRK: Thank you, Jeff.

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