February 2010 Issue | Jan Marino Ramirez, PhD Director, Center for Integrative Brain Research

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Welcome to *Functional Medicine Update* for February 2010. We have a wonderful issue in store for you that follows-up so beautifully from the previous issue with Dr. Suzanne Craft on Alzheimer's pre-senile dementia and its relationship to insulin signaling. I think you are going to find this month a neuronal gem. Let's move right to our Clinician of the Month.

INTERVIEW TRANSCRIPT

Clinician/Researcher of the Month
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You know how much I look forward to this each month on Functional Medicine Update, our clinician/researcher of the month section. I have been so fortunate over the last several years to have remarkable people share their stories of what I consider to be cutting edge information at the frontier of where medicine is going. That is once again going to be the case this month. It is my opportunity and privilege to discuss with Dr. Jan Marino Ramirez the work that he is doing at the Department of Neurological Surgery, University of Washington School of Medicine and the Center of Neuroscience at Seattle Children's Research Institute in Seattle, WA.

I had the serendipitous opportunity to meet Dr. Ramirez on a plane flight coming back from Chicago when he was changing his place of focus/work from the University of Chicago to the University of Washington and was in that transition phase of taking on this new job as the Director of the Center of Integrative Brain Research at the Seattle Children's Research Institute. We got talking, as is often the case when you have a four-hour flight. If you have a kindred soul next to you, you start a conversation, and as it materialized and evolved, it turned out we had so many points of contact in common. The excitement grew. The four hours of flight time flew by, literally, at supersonic speed. When we landed we recognized that we had been traveling a similar path, intellectually, for many, many years. It was a great privilege to have a chance to meet Dr. Ramirez, who goes by the nickname Nino.

Dr. Ramirez has a background in biology and got his PhD summa cum laude
at the University of Regensburg in Germany. He is a citizen of the world, having been born in Peru, educated in Europe, and working as an academic in the United States, now-fortunately for us-in the Seattle area. Probably his most notable accomplishment that you are going to be hearing about is the discovery that he and his research group have made in the area of epilepsy and seizure disorders. I'm going to let him tell you his story. From this specific example of the extraordinarily innovative and precise research that he has done I think you will see a more general theme about this whole nature of where we are going in basic research: to connect it in a translational way to clinical applicability and ultimately improve patient outcomes in very complex areas.

Dr. Ramirez it is a treat and pleasure to introduce you to the listeners of Functional Medicine Update and thanks for being with us this morning.

JMR: Jeff, this is really wonderful,this introduction. It's a very hard act to follow, but I totally agree we were kindred souls. I never had such a short flight, I must say. The four hours went by like minutes and I learned so much. It is a great pleasure that we can now talk about this whole thing in a different way.

JB: Before we get into the specifics, let me talk about-or let you talk about-your path. I'm talking about your intellectual path that led you to your position at the University of Chicago and, more subsequently now, at the University of Washington School of Medicine. Maybe you could tell our listeners about that and how you got into epilepsy research.

Studying the Brain: From Invertebrates to Mammals
JMR: It was really a crazy situation. I became a biologist because I was very interested in how the brain works. In fact, when I started off, I thought that we would never understand the human brain because it is way too complicated. I started to work, in fact, on insects because we thought these are very, very small brains, very clear-cut behaviors, and we will be able to understand it. We actually made really good progress in understanding the plasticity of those neural networks-the dynamics, how they adapt to behavior. At one point, I got kind of a midlife crisis because I thought, "The principles that we find here should also be applicable to the mammalian system and to my sense of humans." I saw so many similarities that basically, mid-career, I switched my science from working on invertebrates to the mammalian system. It was a very high risk jump because I was kind of established in one field and invaded another field, but within one year we made huge progress in the neural control of breathing and, indeed, all of the principles that we learned in the invertebrates helped us, very much, to really go very deep into a better understanding of the dynamics of the mammalian brain.

Nowadays, I think the mammalian brain offers huge opportunities because there is huge manpower behind it. There is so much known about how genes affect the nervous system that I think we are at the edge of a new wave of understanding of how the brain works. Really, my getting into the medical field was coming from the urge to understand how the brain works. I must say this urge is still there.

I am learning so much more about the brain now that I am starting to interact with patients and with clinicians, and I think this partnership is something that helped me tremendously in this path. I have the feeling that right now we are going through an incredible change in how research is working. I say this because I'm just one example of many, many people. The basic scientists, for many years, started to work on the brain with the premise that at one point it would help patients. But really it wasn't clearly meant.

We knew that if we could better understand the brain we would help the patients, but it was such a daring step that we were all scared to go the next step to really help patients.

What happens now is that people get a little frustrated. They put so much money into research, and at one point they want to have a return. There was a huge drive to say, "Hey, guys, now let's go really to the next step and really try to translate the ideas into a cure or therapy." That's when this huge wave of translational research started. I think we're in the middle of a change (a conceptual change). We are realizing that to understand the brain, working with clinicians will help us tremendously because for the children and the adult people with neurological disorders, all of these problems are related to brain function. If we work with them, we get a much better understanding of the underlying mechanisms. What I see as a conceptual change right now is that people have realized that it's not bench-to-bedside work, it is bench-to-bedside-beside-to-bench interaction that has to be taken very, very seriously. Only if you really work together can you get to the next step.

Here, for example, at our research institute, on the same floor we are working with clinicians and we are working with patients. So we work with neuroscientists, but also with patients. That is, I think, the key for a better understanding of brain function, and the cure, in the end.

Grant Titles Indicate an Interesting Body of Work

JB: I think that's a fantastic description of the landscape of what's going on now and what people are calling translational research and translational medicine. I wanted the listeners to get a sense as to what you, over your years of discovery, have been involved with. I'm going to read off, quickly, some of the grant projects that you've had funded. As I go through these titles, I bet our listeners are all going to say, "Wow, this is a very, very interesting area to be involved with." Here's a quick listing. Grants in: Hypoxic effects on mammalian respiratory neural networks; Role of substance P in controlling the central respiratory neural network; Integrated effects of chronic intermittent hypoxia; Pediatric epileptogenesis: from bedside to the bench; Aminergic uptake blocker and the treatment of erratic breathing in Rett syndrome; Neuronal control of pacemaker activity; Cardiorespiratory dysregulation in familial dysautonomia; Genetic analysis of congenital hypoventilation syndrome; Defining the domain of epileptiform brain electrical activity; Hypoxic effects on mammalian respiratory neural networks (ultimately resulted in a completed grant).

When we go through this and we look at apnea and all the other things that your research has touched, it reminds us that you are really in a select group of people doing systems biology research. I bet you didn't initially think of it as such, but you've found yourself in that, and oxygen is one of your principal discovery areas as it relates to controlling many, many functions in the system of these neural nets. Was this a slow, sequential discovery process? How did you get there?

Studying the Brain as an Integrated System: Epileptogenesis

JMR: No. I think from the get-go I was always interested in the systems level. I really wanted to understand how the brain works as a system and I think this integrated thinking helps you to better understand how it works. Just doing genetics or just doing single nerve cells will not get you very far unless you integrate it with a more systems level approach. I think this way of thinking is so much within a person that you cannot change it or learn it. Either you are like this or not. I love complexity, and because I love complexity I tackle complex issues and am able to solve the underlying problems.

One of the grants is about epileptogenesis from bed to bedside. I think this is a very good example of how research brings you further if you interact with patients. We basically started to analyze brain tissue that was excised during a pediatric operation. There are lots of children-like up to 40{56bf393340a09bbcd8c5d79756c8cbc94d8742c1127c19152f4230341a67fc36}--that become intractable and the only way to treat them is to take out the epileptic focus (basically the center for the seizures). Instead of just throwing this brain tissue away, what we did was we used this tissue to better understand the reason. Why is this such an excitable piece of brain tissue? Why is it causing all these problems? In fact, we discovered that even if we take it out of the brain, we can replicate the seizures and that brain tissue responds to the anti-epileptic drugs very much like the whole patient did. We could do drug studies very precisely and we were able to predict what the best medication was for a given patient. That was a very, very rewarding finding for a group of scientists who really started off working on an insect. We were so gratified that we helped several of the patients find the right medication.

But what happened then was after four years, several of those kids started to get seizures again. We realized that finding a new drug that helps to control the seizure is really just the first step and really hasn't tackled the real problem of epileptogenesis. We were in a real big state of frustration because we did our best-these are like 36-hour, non-stop experiments-and we did this for several years, and then we realized the real problem is that this piece of tissue kind of wants to seize. It has this drive to be overheated, to be overexcited, and if you give it a drug that can temporarily abolish this overexcitation, after awhile--because the network or the neurons are set in a different way--you get a seizure again. We realized that what we have to understand is the whole thermostat of regulation in these nerve cells. It is kind of like you are working with a room that is overheated because the thermostat is set at 100 degrees Fahrenheit. What you do at that moment is you open one window to cool the room off, but the thermostat is working and after awhile it gets hot again. So you open the next window, you cool it, and then again. After the third drug, nothing actually helps anymore; the room will be hot and hot and hot. Instead of just opening windows and trying to regulate the excitability this way, we have to understand what is wrong within the cell. What is the homeostatic regulator that controls excitability?

For several very complex reasons, we got into the inflammatory pathway. Inflammation changes the cell, itself, and we realized that basically this inflammatory process that seems to take place in the cell is causing this overexcitability. So we became very interested in the role of antioxidants and things that regulate intrinsic excitability. That's a very, very big topic, as you said. The bottom line is, through the interaction with the patients and the clinicians we were able to change the paradigm of how we should go about studying epileptogenesis. This was a very, very rewarding journey that is a very good example, I think, of how translation works. You don't work just on your bedside and try to understand why there is a seizure, you really work with a patient to get rid of the seizure, and only by doing this you see the whole challenge.

JB: That's a wonderful segue to the visit I had to your facility and talking to your post-doc collaborators and also your seminar that you gave to our research group in Gig Harbor. You made an extraordinary discovery--a model system--for studying the effects of things like oxygen tension and other substances. It is a systems biology approach towards understanding neurological function versus looking, as most neuroscientists do, one cell at a time and trying to understand each cell in isolation. Can you tell us what this discovery was? I know you got national media attention for it and deservedly so. It's incredible when you see your preparation breathing and hiccupping. If you could just tell our group about that, I think it's an extraordinary discovery.

Studying the Effects of Oxygen on the Breathing Center of the Brain

JMR: What you are alluding to is the fact that we can identify the center that controls breathing and isolate it. In isolation (and now we are talking just like a half-millimeter-thick piece of brain tissue), this brain tissue is still generating the principal drive for breathing. So it is generating arrhythmic breathing activity in the dish, and it not only generates breathing, but if you take away oxygen, it will start to generate sighs (like augmented breath that we would also do-when we snore we do this very strong augmented breath) This piece of tissue will not only do this, but if there is really no oxygen, it will go into a mode of gasping and basically this is the last step to get oxygen. So basically this piece of tissue mimics, exactly, what the whole organism would do, and it allowed us to study the whole mechanism-how this neural network that controls breathing reconfigures to adapt to changes in oxygen levels.

That led us to very important insights into, for example, Sudden Infant Death syndrome. We realized that in hypoxic conditions when you do not have enough oxygen, your nerve cells depend on a single kind of mechanism, which is a sodium-dependent mechanism, and this mechanism depends on a certain modelatory environment, which depends on serotonin, norepinephrine, and other things. If you have a defect in one of those, you can breathe perfectly fine, but if you get into this hypoxic condition then your response is wrong.

People might say, "Gasping? Why could this be deadly if you don't gasp?" We have to realize that gasping and the breathing system itself is not just controlling our lungs. The breathing center controls, also, our whole state of mind, so to speak. If you sigh, you activate your norenergic system, you activate your neocortex, and it's an important arousal mechanism. Ninety-five percent of the time when you wake up at night, you wake up with a sigh. It is kind of a wake-up mechanism. If you have a disturbance in those mechanisms, and you lay on your stomach and don't get enough oxygen, then your system will not wake you up and you will basically get brain damage and die, which we think has to do with Sudden Infant Death syndrome. It is, of course, a very, very simplified manner in which I told you this. It is much more complicated, but this is kind of the principle behind this whole discovery that we made.

Discoveries Related to Rett Syndrome

JB: From that, you and I had this moment of "aha" where you had told me about some of the Rett children and you actually showed some videos. I think it was of a couple of young girls who were patients at the center. I then said, "It's interesting because I was involved in the publication of a paper back in the late 80s on Rett syndrome girls, showing that when we looked at complex analysis of their neurochemistry, if we put them in rebreathing situations, we could normalize their neurochemical metabolites." There was almost kind of a convergence between our two world views coming from entirely different perspectives.
JMR: That was a very fascinating example. For the listeners who are not very familiar with Rett syndrome, it is a very devastating disorder that affects primarily girls because the boys basically die very early on. It is associated with a lot of problems, including seizures, but also huge breathing problems. It's totally heartbreaking to see children with Rett syndrome and their breathing problems. At the moment we have no way to control their breathing. Jeff alluded that he was involved in the discovery that there is a problem with the amines, which are the biogenic amines that are present and control the state of the neural network. These children have deficits in this part of the brain. As a consequence, they start to have abnormal breathing problems.

What we discovered is that this is kind of just the beginning of the whole problem. The beginning of the whole problem is that your breathing system is out of balance, and now the breathing system tries to

adjust, but it gets---always--not enough oxygen, which then changes how you respond to neuromodulators. So a substance that under normal conditions for all of us would be a stabilizing substance, now suddenly becomes a disturber of brain function. In awake state we have very regular breathing, but for these children, in awake state, breathing will become very, very irregular because these substances that normally stabilize breathing become destabilized. That was, again, a very interesting interaction with patients that got us there. In the breathing system, when you isolate it, we were able to heal it right away, but in the whole child, we were not able to do that. The reason for this is that the phenotype of these children is really a complex one, resulting from this interaction that is involving, for example, hypoxia-inducible factors like EF-1alpha, etc.

It is very complex research that is also related to obstructive sleep apnea, which is affecting a huge amount of people in the United States (with the crisis of increased obesity, for example). It is a major problem A lot of children (not even obese ones) have sleep apnea. It affects cognitive functions and all of this kind of relates to the stability of neural networks in the brain.

JB: As I read your papers and had the privilege of listening to you talk about your work I was reminded of Glenn Doman and his group's work at the Institutes for the Achievement of Human Potential, where they have been talking (for 55 years) about oxygen in children with brain injuries (that oxygen may be a limiting nutrient). Because oxygen is 20{56bf393340a09bbcd8c5d79756c8cbc94d8742c1127c19152f4230341a67fc36} of the atmosphere, it's like free currency. But their view is if you look at these kids with brain injuries that they have seen over the 55 years that they have been in business and providing these services, many of these children have these temporal ischemic-type things going on, which then produces kind of an induced oxygen deficiency and makes it a limiting nutrient. They have talked about the whole nature of training these children how to breathe. This goes back, actually, culturally. Almost every traditional form of healing has had some way of improving breathing, from yogic, or dance, or exercise-some ways, before intubation, of getting more oxygen into tissues. It seems that you are really hitting on a fundamental mechanism that almost gets us to think that there is no such thing as free currency. We might think of water and air as being free, but yet they can be limiting factors in certain situations, particularly with regard to injury or maybe certain genetic uniqueness.

JMR: You know, I love complexity, and oxygen is one example of complexity because I think one of the key factors of the breathing system is not only that it controls the lungs, but it also controls our neural network, essentially. I think you would always say, "I'm inspired," but you would never say, "I'm expired." It is tuned to inspiration when your respiration network actually drives a lot of neural function. So I think a lot of the healing that you get through controlling breathing is not only the oxygen, but also the central nervous system drive that controls your brain function intrinsically. Oxygen is another very, very complex system because you need a very, very fine balance between too much and too little oxygen. Both are bad, and it is very important that the brain is establishing this balance. I think what happens if you are in a situation where you don't have enough oxygen is that the brain starts to get out of balance and basically runs into catastrophes. It suddenly doesn't respond anymore to normal oxygen as it should. That's why I think maintaining efficient oxygen is very critical to keep the network in balance (the brain).

Inflammatory Processes and the Brain

JB: That takes us back to one of the points that you made earlier: that your research, more and more, is heading down a road to look at certain inflammatory processes going on that relate to redox potential in

the brain, and relate ultimately to things like mitochondrial function, and how that then has an influence on signaling, which then influences neural nets. Can you tell us a little bit about what that environment looks like for you?

JMR: There are somewhat interesting things about it. Here's the situation: The respiratory system is extremely sensitive to reactive oxygen species. You put on hydrogen peroxide (or whatever), and it responds very, very much. We thought, "Oh well, it is damaging the brain." But it did not damage this part of the brain. It was just a signaling molecule, as a signal for changing activity in the brain, whereas, say, in the hippocampus in the neocortex, if you do the same thing, actual nerve cells die. Basically, in different areas, the role of oxygen is very, very different and there are very complex adaptations going on that play a role in regulating activity and we are trying to decipher this.

JB: Last month in Functional Medicine Update we talked with Dr. Suzanne Craft, who is actually one of your colleagues at the University of Washington. Dr. Craft's work is looking at what she called "type 3 diabetes" and its relationship to Alzheimer's dementia and pre-senile dementia. The concept that is emerging from her work is that amyloid plaque, in part, relates to insulin signaling dysfunction that is associated with hyperinsulinemia and pre-diabetes (type 2), or even so-called metabolic syndrome. When I listen to her talk about her extraordinary work, the mechanism by which some of these things occur in terms of brain dysfunction, hippocampal apoptosis, and so forth, it seems to tie very closely together with what you're talking about in terms of oxygen delivery and respiratory networks, and neuronal bioenergetics. It seems like the domain that is emerging from members of this community from multiple disciplines is starting to come to kind of a consensus as to how these things might interrelate through different signaling networks.

Mitochondria and Neuroexcitability

JMR: Absolutely. The importance now becomes much more recognized than it was before. We always thought neuroexcitability of a nerve cell was determined on the surface of the cell. There are these ion channels that change excitability, but we didn't really realize the importance of the mitochondria within the cell-how they relate to excitability. And there is increasing evidence (and I think we don't quite understand how it works) that the mitochondria itself has oscillations that actually determine the health of the nerve cell. People are thinking that a lot of the excitotoxicity comes through this oxidative stress that is produced within these mitochondria, and it might relate, for example, to Parkinson's disease, because we still don't understand why, in Parkinson's disease, one cell particularly dies. These are cells that have intrinsic mitochondrial oscillations that seem to be critically involved. I think we are getting better and better insights into the role of energy metabolism in regulating the health of the single nerve cells and I think we totally underestimated this so far.

JB: There is one other name that I am familiar with in the area of epilepsy research. This is an investigator from Montreal, Andre Barbeau. I'm not sure if you are familiar with his name. He worked a lot with his group on taurine as kind of a conditional nutrient that he was able to show (at least in a book that he published a number of years ago) could influence epileptic seizures in animals (this was an animal model) and then actually did some human clinical work showing that certain types of seizures, when taurine was supplemented as a conditionally essential nutrient, they had clinical improvement because of changing polarization and bioenergetics of the centers. It raises the potential that there may be therapeutic agents that focus on the cause rather than the effect of epilepsy that are yet to be discovered. Do you have some optimism that this could be the outcome?

JMR: I think what we need to understand is basically how those channels for excitability and also the intercellular membranes are regulated. The membrane (the lipid bilayer, and all the surrounding ion channels, and kinases, etc.) is a system on its own. They are very, very complex. They are like these lipid rafts and all these interactions between the lipid bilayer and those really functional units depend on a lot of factors. We talked about omega-3, for example, playing a big role in stabilizing membranes, but also in regulating, in the end, excitability. I think we are just touching this area and realizing how much more regulatory processes take place in a nerve cell at this level that we took for granted. We thought, "Oh well, the cell has ion channels." But we didn't know that they are basically embedded in a very complex network of molecules, and if one of those molecules is not fed well (if it is missing something) then you have huge consequences. I think that is also an emerging field of research.

JB: I can't tell you how much we've enjoyed this discussion. Obviously we've prospected in all sorts of extraordinary areas that I think, in the traditional sense of neuroscience as it was seen 10 years ago, might have been considered risky, and so this has been kind of a courageous discussion that I have taken you into and I thank you for your willingness to go there. The courage is really your's because you've moved your whole professional career from Chicago to Seattle, and you have started to assemble your team there at the center and decided that you wanted to do integrative neuroscience research, which illustrates your willingness to prospect new areas. Have you had much pushback at all from this, given that you are the guy in charge now and kind of assembling the team?

JMR: If you make a decision full-heartedly, you cannot do something else. As soon as I realized that in order to do really good translational research I had to be much closer to clinicians and patients, I had basically no other choice than to come here to Seattle Children's Research Institute because this was a great model for translational research. I must say I was very scared, but everything was like 10 times better than I expected (and I expected a lot). It is really an amazing environment in which to go for it. I think I have to tell anybody who is scared to go the next step. If you full-heartedly believe in something, that's what you have to do. I'm extremely happy that I made that step. It invigorated my science so incredibly much, and I think we have made huge progress in the one year since I arrived. I must say, I am totally hyper about it.

JB: I hope everyone who is listening feels that sense of inspiration. Each one of us, in our little island, carves out our trajectory in life. I think that what your model demonstrates to each of us-those clinicians who are seeing patients in their office-is that every day they are pioneers. They are creating new ground, and how they look at that patient and look at their work will create a sense of its outcome. I really want to thank you so much, both for the specifics of what you shared with us, but also for just the general concept of being bold and courageous about taking on new responsibilities and bridging the gaps that some people are very fearful to bridge between basic science and the clinical outcome. I think it's a statement of the new age in the 21st century to create a functional medicine. Thank you, Dr. Ramirez, so much.

JMR: Thank you so very much. It is always a great pleasure to talk to you.

I hope you enjoyed that discussion with Dr. Ramirez as much as I. That was an unbelievable kaleidoscope of visionary thinking and translational research. Let me give you, my summary takeaways as to how, as a clinician, particular information that Dr. Ramirez shared might be of value to you.

Summary of Interview Takeaways

I think the first and most obvious takeaway is that to understand complex physiology, we can't think of single cells working in isolation. His work on the brain slices he mentioned provides an understanding of how, even at a holographic level, a system of different cells working together kind of mimics and recapitulates that a whole organism breathes, gasps, snores, and hiccups is a very interesting part of our understanding. In fact, he didn't mention it, but he connects these half-millimeter-thick cell slices across the tissue into a device that produces (from their electrical changes) a sound, so you can actually hear, as he said, these slices breathing, and you can hear them gasping, and you can hear them hiccupping. It's a pretty remarkable metaphor to understanding systems and you can't understand one cell type in isolation. For example, you can't just take the nigra cells in the area that is associated with Parkinson's and understand that without looking at the whole system. This concept would be the number one takeaway.

The number two takeaway for me is the fact that there are a very important series of controlling factors for this system of neurochemistry that relates to oxygen delivery and powering up reduction oxidation through mitochondrial bioenergetics. We should not forget the importance of breathing and exercise and oxygen delivery to tissues. This is, of course, what Glenn Doman at the Institutes for the Achievement of Human Potential has been talking about for over 55 years. They train children to be more neurologically high performance. This process has to do with all sorts of technologies that might improve oxygen delivery (not just physical training and exercise), but also aspects of oxygen-carrying capacity in the blood, and even the CO2/O2 levels that help to use the bore effect to drive oxygen into tissues. That is possibly one of the reasons why rebreathing some exhaled air that has more CO2 in it can help to train brain centers to be more respiratorily active. This is, of course, one of the techniques that is used at the Institutes for children with certain brain injuries to improve their function. So oxygen could be seen as a limiting nutrient, and it could be a very important part of any therapy. Of course, there are all these traditional historic healing methods that are ways of improving oxygen delivery. I think that's concept number two in the takeaways.

Number three for me in the takeaways is the recognition that there are many structural components within the complex neural network that are regulated by aspects of nutrition that can improve depolarization and intercellular signal transduction and communication among complex cell types in the nervous system. Dr. Ramirez mentioned the essential fatty acids (DHA) that make up such a great percentage of the two position of phospholipids in the brain membranes. We must think about the important role that proper omega-3 fatty acid nutriture plays. We must think about the appropriate role that things like carnitine and taurine and lipoic acid play in modulating aspects of neurochemistry and oxidative reductive chemistry in the brain, which is the center of very high oxygen tension with very little antioxidant protection, so to speak, and that's why it may so reactive-oxygen-species sensitive, as Dr. Ramirez talked about.

The next and final area Dr. Ramirez talked about--the inflammatory process--comes back once again to the yin and yang of inflammatory balance. As we get into a place where we have too many proinflammatory mediators, we start shifting the sands of physiology into a different signaling network that is associated with depolarization of membranes and changes in ion transport and ultimately, in the case of epilepsy, different kinds of physiological phenotypes. I think of those characteristics that are all modifiable and all the things that we can think about when we are looking at patients with complex neurologic problems. Of course that ties back to Suzanne Craft's work that was mentioned last month, with insulin signaling and how that affects bioenergetics of the brain and ultimately regulates certain aspects of oxidative chemistry.

We are starting to develop a new functional medicine approach toward the understanding of the origin of a whole array of complex neurological disorders. I don't think we are treating one at a time. In fact, as Dr. Ramirez pointed out, using drugs to treat one condition at a time leads to drug resistance because we didn't ultimately treat the cause, we were treating the effect. You can see that in cell slices as well as in human beings.

Epigenetic Side-effects of Common Pharmaceuticals

These factors of resistance that occur to medications over time, in which the body adapts (probably epigenetically) to the exposure to certain medications, blunts their effectiveness and requires finding new molecules that are new to nature to modulate function. There is a constant concept of manipulating the therapeutic materials or intervention to keep up with the body's ability to adapt or to modulate its function upon exposure to a foreign molecule. I'm reminded of a recent paper that was authored by Moshe Szyf and Antonei Csoka at McGill University (the Division of Pharmacology). They have been actively involved in looking at the role that various substances have on epigenetic modulation of genetic expression and this recent paper is titled "Epigenetic Side Effects of Common Pharmaceuticals: A Potential New Field in Medicine and Pharmacology."[1] In this article what they write about is that over time, exposure to new-to-nature molecules can induce, in the epigenome, modulation of epigenetic marks, so that ultimately gene expression patterns change. This could ultimately be seen as changing drug sensitivities, or changing drug tolerances, or even changing drug efficacy or safety relationships.

DNA and chromatin modifications that persist from one cell division to the next occur as a consequence of these epigenetic marks and are related in part to exposure to foreign molecules like drug molecules. Over time, this may make an individual less tolerant and more sensitive to a drug. An example of this would be some of the anti-rheumatic drugs that are used for things like systemic lupus erythematosus and rheumatoid arthritis. Over time, some of these medications may actually start to become intolerant to the patient and induce toxic molecular effects, even though they may have had a better safety tolerance to begin with. I think this concept of a relationship between epigenetic marks and therapeutic foreign molecules is very interesting and may help us to better understand why drugs may lose effectiveness in the way patients respond to them. In the case of children with various types of neurological issues such as epilepsy, as Dr. Ramirez talked about, they have to have their medications constantly changed.

The neuron, when it has these disturbed aspects of intercellular signal transduction and communication, really responds to a defect at the cellular level. Often what these drugs do is treat at the cell membrane level by blocking or inhibiting certain functions, but the real origin of the problem is a disturbed metabolism at the neuronal cell. As Dr. Ramirez talked about, neural networks are very responsive to reactive oxygen species and mitochondrial phosphorylation-type reactions.

It is a bioenergetics story. When we start looking at the principal contributions to dysfunction, the functional medicine model once again holds true for neurological illness, I think, because what we are talking about is looking at the root causes of how the cellular pathology or cellular dysfunction ultimately promotes secondary adverse effects within the cell membrane such as gradient changes, transport properties, intercellular signal transduction and gene expression alterations. Each of those outcomes could be treated with different molecules that block or inhibit certain function. What factors might alter mitochondrial function? What type of functional changes increase reactive oxygen species and shift the redox potential into an oxidative mode with increased free radical pathology? I think these are important

questions to be asking clinically. It leads us to things like coenzyme Q10, and N-acetylcysteine, and N-acetyl-L-carnitine, and taurine, and various types of conditionally essential nutrients that might be very helpful for modulating certain aspects of mitochondrial bioenergetics. We could use the term "antioxidants" in the broadest sense, but I don't think "antioxidants" is really a specific enough term because in this case what we are really talking about is neuronally specific active substances that serve as cofactors or facilitators for proper mitochondrial redox function (reduction/oxidation function).

Early Screening Tests for Dementia: Genetic Tests Don't Tell the Whole Story

Clearly, the earlier one can be involved in understanding the trajectory toward these problems and intervening at an earlier stage, the better off for the patient and the more likely that the intervention can be more physiologically based rather than focused on modifying symptoms by "hard-hitting" inhibition. To talk about early assessment, let's use Alzheimer's dementia as an example. There are useful assessment tools that can be used well before a tertiary stage of Alzheimer's disease, where even with the best therapeutics effective outcomes are limited. Are there useful early warning screening tests? We have heard about lab tests like the apo E4-type genetic test to look for alleles that are associated with increasing risk to cardiovascular and Alzheimer's disease. But a genetic test in and of itself doesn't tell you about the phenotype of the individual because one might carry a specific genetic risk factor in his or her genotype, but it may not be expressed in the phenotype. Another individual may have a lower risk factor, but if it's more amplified in its expression, it could have a more dramatic effect on the outcome of the phenotype. That means, in this case, Alzheimer's disease.

Although dementia is common with an expected prevalence of about 13 in 1000 people, aged 65 – 69, and 122 in 1000 of those over 80, only about half of those affected are diagnosed. We are always looking for new ways of getting early warning information that might then be more amenable to a more mild intervention. Various types of tests have been developed-psychometric questionnaires-to test things like short-term memory. A recent test that has been published, which I think has some very interesting opportunity to be used routinely in the clinic, is a pen-and-paper test that is a self-administered cognitive screening test. This cognitive screening test was first described in detail in the *British Medical Journal*.[2]This test was developed at the Department of Neurology at Addenbrooke's Hospital in Cambridge. I think you'll find this to be a very interesting type of pen-and-paper screening test. It is simply done. It seems to have a very good clinical sensitivity. It seems to move back the threshold for assessment to a much earlier age. This is the so-called TYM test, which stands for "Test Your Memory."

I thought the results of this study on the TYM tests were quite remarkable. Control participants completed the Test Your Memory questionnaire with an average score of 47 out of 50, whereas patients with Alzheimer's disease scored, on average, 33 out of 50. They found that the Test Your Memory score showed excellent correlation with two standard tests, a correlation of about 42 out of 50 had sensitivity of 93{56bf393340a09bbcd8c5d79756c8cbc94d8742c1127c19152f4230341a67fc36} (when anyone had a score at 42 or less out of 50 of the questions they had a sensitivity of 93{56bf393340a09bbcd8c5d79756c8cbc94d8742c1127c19152f4230341a67fc36} on specificity, but 86{56bf393340a09bbcd8c5d79756c8cbc94d8742c1127c19152f4230341a67fc36} in the ultimate diagnosis of Alzheimer's disease). The Test Your Memory was more sensitive in detection of Alzheimer's disease than was the Mini-Mental examination, which is often the test that is used clinically (TYM detected 93{56bf393340a09bbcd8c5d79756c8cbc94d8742c1127c19152f4230341a67fc36} of patients compared with 52{56bf393340a09bbcd8c5d79756c8cbc94d8742c1127c19152f4230341a67fc36} for the

Mini Mental State examination). The TYM test had a much higher level of sensitivity in picking up pre- and early-stage Alzheimer's disease.

The Test Your Memory test is available in the article (it can be printed out), and it is basically a simple type of memory test that a person fills out and does on their own (it is self-scoring). It is almost fun to do. (I guess it may be less fun if one has a very serious cognitive impairment; maybe then it is very challenging.) I think we are moving in the direction of having validated tests that can be used for earlier assessment of dementia, which would be very helpful in intervening with more mild types of interventions, and also for following and tracking the success of therapy. For those of you trying to find this questionnaire, it is the June 13 issue of the *British Medical Journal*, on page 1398. You can even Google "Test Your Memory" and probably be linked directly to it. The Brown paper (the specific article that has the Test Your Memory reference in it) is in that same issue of the *British Medical Journal*.[3] I hope this questionnaire might be helpful for you as you are trying to develop some tools in the clinic for evaluating early-stage dementia.

I have talked about two things, one of which is an assessment tool. The other is epigenetic effects and what happens as patients become tolerant to one drug (possibly by epigenetic modulation), which then changes the sensitivity to the medication, and may in some cases make them so sensitive that a drug that was previously tolerated now becomes toxic. This epigenetic correlation really links back to our emerging understanding of the etiology of Alzheimer's. It would be a little bit premature to say that this is all linked together and we've got it completely nailed down and all aspects of this etiology is well understood. But certainly the map-or let's call it the grid-of understanding is gaining more density and more degree of mechanistic understanding.

Part of this emerging understanding has to do with the tau protein phosphorylation and how that relates to amyloid peptide aggregation, and ultimately the formation of neurofibrillary tangles and the tau hyperphosphorylation, which is a post-translational, kinase-modulated process that has to do with activation of inflammatory and oxidative pathways. It ties back, also, to epigenetic marks. It has now been found, for instance, that elevated homocysteine is a surrogate indicator for alterations in the tetrahydrofolate cycle, which is a methylation cycle. As that occurs, there are alterations in epigenetic marks related to methylation of the genome, and that then ties together with protein phosphorylation alterations and protein methylation alterations that ultimately create different expression patterns. There is a methyltransferase alteration that links homocysteine metabolism with tau and amyloid precursor protein regulation and tau hyperphosphorylation, and ultimately amyloid precursor protein aggregation the formation of neurofibrillary tangles. This is kind of-again-an emerging mechanism that ties together a precursor marker, which could be considered a surrogate biomarker (hyperhomocysteinemia with a mechanistic correlation with epigenetic alterations in methylation patterns), and how that ultimately transitions itself into different intercellular signaling processes through phosphorylation and regulation of various bioactive peptides, including tau, and how that then correlates to things like the triggering mechanism of oxidative stress and alterations of mitochondrial bioenergetics in the neuron.[4,5]

This pattern-this mechanistic understanding-fans out into a more functional medicine-based landscape, in which we have to look at many different variables and ask the questions: Is there a genetic underpinning? Does that person have a familial tendency toward accumulating homocysteine as a surrogate biomarker that relates to alterations in methylation patterns? Are the methylation patterns that that person has that are controlled by their genes or by the genes in combination with the environment, like drugs, or

chemicals, or substances that might modulate the role of the body in its response to those exposures? Do they have adequate levels of specific nutrients to modulate the throughput of these intermediaries (in this case, folate, B6, B12, betaine), which we all know play important roles in the tetrahydrofolate cycle? And then ultimately, how does that relate to the exposure to even pharmaceutical agents that might be used that are potentially going to impact epigenetics and create different gene signaling processes that then alter methylation and phosphorylation patterns? I think you can start to see that we're spreading our knowledge base into a broader landscape that allows us to better understand (possibly) the etiology in that patient, looking at their genes (their genetic architecture) and their environment to come up with a model as to where the modifiable factors might result in that individual's specific history and tying that together with an assessment tool (like the Test Your Memory assessment tool) that allows us to track, clinically, how effective our intervention is being responded to by the patient.

Insulin Dysfunction, Inflammatory Signaling, and Oxidative Chemistry

One of the major environmental modifiers of this whole process is insulin, which we discussed in a previous issue with Dr. Suzanne Craft. I want to come back and remind us of the importance of this topic because one of the wild cards is the insulin signaling pathway and all the variants that are tied into it, which include things like inflammatory signaling and even oxidative chemistry, which are all tied through to the insulin axis of regulatory control and insulin-like growth factor 1 and all the various types of other intermediary molecules and enzymes that are involved in the regulation of bioenergetics through glucose metabolism. In tau hyperphosphorylation, one of the distinct mechanisms that comes up is not only the homocysteine connection, but also the insulin dysfunction connection. In the *Journal of Neuroscience*, there was a very interesting paper looking at Alzheimer's disease characterized by this extracellular aggregates of the beta-amyloid peptide and how the intraneuronal neurofibrillary tangles are composed of hyperphosphorylated tau protein assembled in paired helical filaments, and that this tau hyperphosphorylation can induce aggregation and are thought to induce neurofibrillary tangles and neurodegeneration in Alzheimer's disease.[6] This has now been tracked to be precipitated (this whole process) by alterations in insulin signaling (so-called insulin resistance hyperinsulinemia). I've just come back into the environment or the domain of Dr. Suzanne Craft, our previous researcher-of-the-month. Insulin dysfunction can induce in vivo tau hyperphosphorylation and ultimately travel through neuronal function into the production of neurofibrillary tangles.

Tau Hyperphosphorylation is Induced by Two Distinct Mechanisms of Insulin Dysfunction
Data indicate that insulin dysfunction induces abnormal tau hyperphosphorylation through two distinct mechanisms. One mechanism was consequent to that of oxidative stress and relates to alterations in phosphatase activity and alterations in phosphorylation activity, which then results in this tau hyperphosphorylation and production of aggregates of beta-amyloid peptide. You might say that's very interesting, mechanistically, but how does that tie, really, to the clinic? What's the takeaway to the patient? Let's first go to some recent studies done in animals that kind of-I believe-point us in the direction. The first is this paper that was out of the University of Oxford, Department of Experimental Physiology and Psychology, looking at the deterioration of physical and cognitive performance in animals after a short-term high fat feeding, in which this high fat feeding induced alterations in biochemical energetics, mitochondrial dysfunction, oxidative stress, increased ROS (Reactive Oxygen Species) production, and insulin resistance and hyperinsulinemia.[7]

Rats generally do not consume a lot of fat in their diet. This study involved force feeding animals into a

high fat feeding regime for just 9 days, and the researchers then looked at the surrogate markers for mitochondrial bioenergetics: uncoupling protein 3 activity, mitochondrial oxidative stress, and also mitochondrial ATP production. They found that this high fat feeding over a fairly short period of time induced insulin resistance, altered the ATP-to-ADP ratios, enhanced the uncoupling protein 3 levels in mitochondria leading to more oxidative stress and more reactive oxygen species, and ultimately was tracked to reduce the cognitive performance of the rats in Mays tests. Within 9 days, these animals started having cognitive dysfunction; they couldn't find their way through the maze effectively.

What does that mean for people eating high fat meals and high sugar meals every day? Do the results of this short-term high fat feeding study in rats translate to humans? Are people consuming these types of diets like long-term high fat/high sugar feeding studies in humans where the ability to go through the maze of life is reduced, as well as the ability to make appropriate judgments and decisions and use the full impact of brain? Over time, does that track against people with certain genetic susceptibilities to increase loss of cognitive function by neuronal apoptosis and cellular suicide, all initiated by these alterations in mitochondrial bioenergetics?

Diet and Cognitive Function

I know I'm using some fairly broad language here. I'm speculating about many things that are not fully bolted down yet. However, as we recognize from some good epidemiological studies published in a whole variety of journals, there does appear to be something consistent that is emerging about diet and cognitive function in humans. Let me remind you all of a recent paper that appeared in the *Journal of the American Medical Association* titled "Adherence to a Mediterranean Diet: Cognitive Decline and Risk of Dementia."[8] This is a clinical outpatient study of 1410 adults greater than 65 years of age in France. The study authors looked at the influence that adherence to a low glycemic load, Mediterranean-type diet versus and ad lib diet had on change in cognitive performance and the risk to dementia over a period of time. They found that higher adherence to the Mediterranean diet, which is associated with better glycemic control, better insulin regulation, and lowered insulin resistance was associated with slower Mini-Mental status examination cognitive decline. Higher adherence didn't necessarily associate itself with risk to incidence of dementia, but because this was a period of time that might have been too short to fully understand the long-term outcome of the effects of a low-versus-high glycemic load, Mediterranean-versus-non-Mediterranean diet, all we can do is suggest the trajectory is moving in the right direction for people who self-administered and self-complied with a Mediterranean diet.

The findings from this study tie together with some other papers that have been published in the same area. One paper appeared in the *Annals of Neurology* in 2006 and was titled "Mediterranean Diet and the Risk of Alzheimer's Disease."[9] This was an epidemiological study of 2258 community-based, non-demented individuals in New York state who were followed for one-and-a-half years, who either self-complied with a Mediterranean diet or just stayed on an ad lib diet. Researchers followed these individuals over a period of time, looking at the appearance of Alzheimer's disease, and found a very significant divergence between the two groups relative to their prevalence of Alzheimer's disease, with the ad lib diet group having a much higher prevalence over a period of one-and-a-half years than the individuals who complied with the Mediterranean diet.

Similarly, there was a study published in the *Archives of Neurology* in 2009.[10] In this case, the researchers were not looking at Alzheimer's, but at mild cognitive impairment in individuals who consumed the

Mediterranean diet versus ad lib diets (again, this is a population/epidemiological study). The adherence to the Mediterranean diet, in this case, was also associated with a trend for reduced risk of mild cognitive impairment. If you consider mild cognitive impairment as a precursor to later-stage conversion to Alzheimer's disease, then the suggestion from this paper is that there is a lowered trajectory or risk toward Alzheimer's disease.

These three papers-the *JAMA* paper, the *Annals of Neurology*, and the *Archives of Neurology*paper-all tie together with this concept of improved insulin signaling, improved neuronal mitochondrial oxidative chemistry, redox potential, and bioenergetics and lowered incidence of alteration of genetic expression, intercellular signal transduction, inflammatory markers that lead to neuronal injury.

What happens if you go to humans, not animals, and you start a short-term overfeeding study, in which you start feeding high fat, high calorie density diets to humans? These studies are now being published and I think are also very illuminating. Let me cite one that I think illustrates the principle. This is a paper that came from the Department of Clinical and Experimental Medicine, Diabetes Research Center, at University of Linkoping in Sweden, looking at short-term overfeeding and its relationship to induction of insulin resistance in relatively lean human subjects.[11] In this case, the researchers intentionally asked individuals to consume high fat diets, and then looked at various aspects of insulin signaling, like insulin receptor substrate activity. They looked at biomarkers of metabolic syndrome, and they looked at kinase signaling through map kinases and ERK 1 and 2, and how they related to this dietary change. This short-term overfeeding study in humans was found to produce an effect on reducing insulin sensitivity, increasing insulin activity, and altering insulin signaling that was comparable to the study that I mentioned earlier about deterioration of cognitive performance in animals that were administered a short-term, high fat feeding diet.

I hope you can see there is some kind of a story that is emerging here that relates to signaling, and alteration of neuronal function, and insulin resistance, and oxidative stress, and inflammatory markers, and neuronal apoptosis, and hyperphosphorylation of tau, and beta-amyloid aggregation, and formation of neurofibrillary tangles. We are really talking about nutritional programming and how that may alter genetic susceptibilities in the expressing of phenotype that is associated with a trajectory toward Alzheimer's. Our ability to understand this early may, in part, hinge on the appropriate types of evaluative instruments or tools that we use to establish functional impairment prior to the onset of a strict diagnosis. That's why the Test Your Memory questionnaire might be one part of this story, as well as other types of neuronal functional challenge tests that allow us to assess neuronal memory reserves and how these functions at the whole organism are related to alterations at the cellular level. That truly is the functional medicine model, I believe, as applied to this area of neuronal dysfunction.

Nutritional Programming and Metabolic Syndrome

There is a very nice paper that talks about nutritional programming and its relationship to metabolic syndrome and to insulin resistance and intercellular signal transduction, which travels through different cell types as inflammatory signaling or alterations in epigenetic programming. This paper appeared in *Nature Reviews of Endocrinology* in the November 2009 issue.[12] When we are in that moment within the exam room with a patient, these discussions that we're having about early-stage memory loss and concerns about Alzheimer's translate to the bottom line of looking at diet, looking at lifestyle, looking at how these variables influence dramatically (over time) aspects of the phenotype that ultimately regulate

the potential risk to a later-stage disease for which the therapy is at best limited right now.

Let me talk a little bit about this nutritional programming concept as it pertains to metabolic syndrome. As you probably all well know-we've talked about it at length within *Functional Medicine Update* over the years-metabolic syndrome, characterized by insulin resistance and altered insulin signaling and hyperinsulinemia, has a variety of hallmarks in the patient that you can see. One indicator is generally central obesity (but not always, I might add, because there are metabolic syndrome patients that are rather low in their BMI). We see a modest hypertension. We see some dyslipidemia that is generally associated with increased triglycerides and a lowered HDL level. And we often have a concomitant factor of increased inflammatory biomarkers like high-sensitivity CRP, which is often elevated. This is certainly true in those individuals who go on to have cardiometabolic syndrome, with a principal risks to cardiac disease.

We also see altered vascular endothelial function, so flow-mediated dilation is often impaired in these patients and that in part relates to their marginal hypertension. If we look at the range of effects that these dysfunctions can have, obviously it ties itself together with all the vascularity, including vascular function as it pertains to central nervous system function. We have this dementia and Alzheimer's connection to insulin resistance that Dr. Suzanne Craft was talking about. We've got the sleep apnea connection that's very tightly tied to this. And we've got the erectile dysfunction family of disorders that are also endothelial dysfunctions and related to cyclic GMP alterations and G-protein signaling and how that ties to hyperinsulinemia. So a variety of different clinical presentations: sleep apnea, erectile dysfunction in males, memory loss, mood swings, energy problems, increased oxidative stress, problems of retinal function, even skin elasticity problems and alterations in skin, texture, tone, and integrity. All of these, with microvascular changes, are related to insulin resistance.

Nutritional programming of metabolic syndrome, although it is a very esoteric title, really spans out into many different important clinical observations that you make in those patients. When you look into their eyes, or you look at their skin, or you look at their blood values, their biochemistry, their body shape-all of these things are tied, in part, to altered distortion of the metabolic web, which then creates this outcome of multiple presentations. It is obviously hard to see within their brains and to understand the neurological implication of this, but over time-not days, not weeks, not months, but generally years, if not decades-of altered insulin signaling, what can happen (particularly in individuals with specific genotypic susceptibilities) is it can induce these problems we are talking about that are ultimately related to neurofibrillary tangles and neuronal apoptosis and ultimately cell death with lowered neuronal reserve.

If Your Patients Eat, You Are Doing Nutritional Therapy

Nutritional programming is a conceptual approach that I think plays a very important role in our therapeutic decisions. Often I'll talk to a physician and they'll say, "I find this interesting, but I actually don't do any nutritional therapy in my practice. I think it's an interesting concept but I'm really not involved with nutritional therapy." And my question is, "Do your patients eat during the course of whatever therapy you employ?" And of course if they are being honest their answer is, "Yes, my patients eat regularly." And then my response is, "Well then you are doing nutritional therapy in your practice. You're just not controlling it."

One of the more important variables that might alter the outcome and success of whatever therapy you select is diet. Nutritional programming alters the whole landscape or architecture of how a person is going

to respond to whatever you decide to do for them. You are basically not controlling a variable that may have a dramatic effect on the outcome of their success. I think putting it in that context turns it around a little bit because in essence every physician does nutritional therapy whether they know it or not. It's an ad lib part of an underlying variable that is modifying what they do. If you are really concerned about optimizing successful outcome, then it seems you would want to control diet and activity levels just as you'd want to control compliance and adherence with your primary pharmacotherapy.

What this *Nutrition Reviews* paper really addresses is how metabolic syndrome, characterized by this clustering of clinical cardiovascular risk factors including hypertension, central obesity, dyslipidemia and inflammation, hepatic steatosis, oxidative stress, and insulin resistance ties together with proper nutritional programming of gene expression, and proteomic and metabolomic outcomes that translates into the phenotype. Different dietary personalities or different dietary constituencies play a very significant role in modulating those influences.

In fact, what we really might start talking about when we look at diet and its relationship to neurological dysfunction, specifically, is that we are in an era of proteomics in which we are starting to recognize that these signals that we are sending through diet get translated, ultimately, through gene expression patterns into mRNA, which then gets converted in some fashion at the ribosome into native proteins and enzymes that control metabolic function. These then ultimately can be post-translationally modified by glycation, or oxidation, or phosphorylation into the final proteins that ultimately regulate our function. So when we are thinking about the clinical strategy toward the patient who is early stage and starting to lose their memory, we ought to really be exploring what it is that is altering the functional integrity of their web of neuronal function (bioenergetics) that is modifiable on the basis of our intervention, and, in fact, is possibly related and focused on the modification of those primary factors that translate into cellular dysfunction that creates the tissue dysfunction that ultimately is seen as this dementia problem (this loss of memory-cognitive decline).

We are in an era of proteomics: understanding this complex matrix of how these proteins that come off our genes are controlled and regulated and how they ultimately regulate metabolic function. If we think of diabetes as a state of altered endocrinological function, we really need to expand that to talk about it as an altered state of physiologic cellular function at the bioenergetic level, at the level of second messengers, at the intercellular signal transduction level. Diabetes is really just a name that we have applied to a very dramatic distortion of the web of physiology that is really an energy deficit disorder if we think about it. Those cell types that are most dependent upon glucose for their metabolism are the cells for which the regulation of this function might be most dependent, so think of where those cell types are.

We recognize that the brain cells are principally nourished by glucose. Only in states of starvation do they shift over into ketone bodies as a substrate for energy. So the brain, although it represents less than 5{56bf393340a09bbcd8c5d79756c8cbc94d8742c1127c19152f4230341a67fc36} of the body weight, consumes almost 20{56bf393340a09bbcd8c5d79756c8cbc94d8742c1127c19152f4230341a67fc36} of its oxygen in glucose. It is a very voraciously hungry tissue for glycolytic reserve (glycolytic energy). When we start altering, then, the intercellular signal transduction, we distort this web. We have a stress put on the system , and the metabolism, and the gene expression, and the proteomic activity shift to respond to that stress and now we start moving into this era of what we call a disease. And it spreads out into all sorts of other companion diagnoses: renal failure, retinopathy, erectile dysfunction, NASH (non-alcoholic steatohepatitis), relationships to Alzheimer's dementia. In other words, all of these conditions fan out

from the central feature of distortion of this bioenergetic status.

Link Between Telomeres and the Biological Aging Process
Lastly, I want to emphasize these things tie together with increased oxidative stress and inflammatory markers, which then causes injury to our genome and can reduce the length of our telomeres. We recognize now that these telomeres that protect the ends of our chromosomes are tied very closely with our biological aging process. There are articles about the association between telomere length and mortality in people aged 60 years or older. In short, telomeres are found in patients with vascular dementia, which indicates low antioxidant capacity. Telomere shortening, as a consequence of these inflammatory oxidative reactions that come from dysinsulinism and altered insulin signaling are associated with cardiovascular disease and Alzheimer's dementia and increasing genetic risk of people like apo 4s.[13,14,15]

I hope I have given you some clinical news-to-use with a patient when you are sitting in the exam room. How do we assess cognitive function? What do we think about in terms of intervention? What's the landscape of modifiable factors that we have available at our disposal as a functional medicine practitioner?

Thanks for being with us. We look forward to sharing with you next month.

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