April 2013 Issue | Shalesh Kaushal, MD, PhD Vitreoretinal Consultant, VRMI

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Welcome to Functional Medicine Update for April 2013. You know, we're having a virtual epidemic—what I call almost a silent epidemic—of an issue that's very, very serious in our global healthcare community, and that's blindness in the adult population. And it's not congenital blindness. This is what I would call induced blindness through what has often been termed age-related macular degeneration.

We're very fortunate this month to have an expert in the area of ocular health and ophthalmological research guide us through this extraordinarily interesting and tortuous field of visual acuity, retinal pathology, and how it interrelates with this rising tide of blindness. This is a very, very serious issue.

As you talk to older people, they'll often say, "If the quality of my life is so depreciated that I'm not enjoying it, then it really marginally evaluates whether going forward is worth it." And one of those things that affects life quality is sight, a virtuous and important function as we grow older (along with memory). As you talk with seniors in settings where there is common communication among people of geriatric age about concerns they have, vision and memory keep coming up as important areas of concern. And these are the areas that are most often impacting older age people, particularly in institutional settings and in various community living situations in which there is a lot of sadness about the loss of vision and the loss of memory that is experienced by older age individuals who are still looking to have some great days ahead in their lives.

Vision and Ocular Health: Connections to Glucose Management, Oxidative Stress, and Mitochondrial Bioenergetics

So what's the cause of this ever-increasing source of age-related macular degeneration and ocular injury that is so serious that vision is ultimately impaired? I call this collateral damage, and it interrelates with insulin resistance, and oxidative stress, and many other topics that we have discussed in *Functional Medicine Update* over the last 30-plus years. In fact, it might be considered the poster child for the outcome from what happens over the course of decades of living where insulin has not been able to properly manage glucose, oxidative stress and mitochondrial bioenergetics are uncoupled and enhanced, and glycation, which is the connection of glucose to various proteins and the activation of inflammatory response, has been occurring for long periods. Eventually, the macula in the eye starts to undergo degeneration, the ophthalmologist predicts that this particular process will lead ultimately to blindness, and the best therapeutic tools we have in terms of pharmacology and surgery are not able to restrain the tide against these processes.

This sounds like an opportunity for lifestyle medicine. It sounds like functional medicine. And it's exactly—I think as I said—a poster child for this kind of intervention. And the collateral damage, which is injury to the eyes, as you're going to be hearing from our extraordinary researcher/clinician of the month, relates to these conditions. Dr. Kaushal can provide both a biochemical perspective, with his PhD in biochemistry, and a medical perspective, with his medical degree and specialization in the fields of ophthalmological surgery and ophthalmology.

Let's—in preparation for this discussion with Dr. Kaushal—talk a little bit about what we have known and what we have learned. I think this is a very interesting topic that takes us back to a period that some of you might remember if you've been in this field for some time and following Functional Medicine Update, because it's been part of our discussions that we've been having since the late 80s. But there was a very important paper that appeared in 1994 in the *Journal of the American Medical Association*, and it was titled "Dietary Carotenoids Vitamins A, C and E and Advanced age-Related Macular Degeneration: The Eye Disease Case Controlled Study Group."[1] You might remember this study; it got quite a bit of press at the time. It was done at the epidemiology unit of the Massachusetts Eye and Ear Infirmary in Boston, and it was published in *JAMA*, as I mentioned, volume 272, page 1413, in 1994. What they were attempting to do is to evaluate the relationships between dietary intake of carotenoids in vitamins A, C, and E, and the risk of neovascular, age-related macular degeneration. This turns out to be an interesting study that probably begs the question: why would anyone want to know what the levels of intake of carotenoids would be relative to the appearance of this age-related macular degeneration? What's the association? Why would you even be led to ask that question? To understand that, we need to go back to look at age-related macular degeneration as a leading cause of blindness in the elderly worldwide. In fact, it affects millions of individuals and the clinical hallmarks of age-related macular degeneration are observed in people in all industrialized countries. In fact, its global cost for management—and as I mentioned, we don't have a good medical treatment really at this point—is over 340 billion dollars annually.[2] So it's a very, very big problem and it's rising in its prevalence.

The majority of age-related macular degeneration patients in the United States are not eligible for clinical treatments, as I mentioned, because we don't have really good late-stage treatments. Therefore, preventive interventions through dietary modulation have become attractive, and strategies are now being designed to try to look at the relationships of specific nutrients and their role in the prevention of injury to the macula.

Understanding the Physiology of the Macula and the Fulvia

Now, it is really important for us to understand a little bit about the physiology of the macula and the fulvia—the center of the retinal area. As you probably recognize, the fulvia is the only tissue in the body that has a color associated with it due to the selective concentration of specific nutrient-related carotenoids, or let's call them xanthophylls, or pigments. The body doesn't make those pigments. This is a very important point. The body concentrates specific pigments that come from our foods, and in this case, those pigments are found mainly in vegetable products

So, individuals said, "Well, hold it. If macular degeneration is associated with a bleaching of the fulvia (meaning loss of the pigments), and those pigments are strictly due to the amount that you consume in

your diet, and we think that maybe as people grow older they don't eat a lot of these dark green vegetables, and red and orange fruits and vegetables, then maybe there is a correlation between the lower level of intake of these specific pigments in vegetable products and the increasing risk to age-related macular degeneration. That was the underlying hypothesis that led, ultimately, to this retrospective study looking at dietary carotenoids in the eye disease case-controlled study in Massachusetts. And by the way, there's a very nice review of the molecular aspects of the pathophysiology of macular degeneration that appeared in *Molecular Aspects of Medicine* in 2012, in volume 33, page 318.[3]

What did they find in the *JAMA* paper? They found that increasing the consumption of foods rich in the carotenoids, and particularly the dark green leafy vegetables that are rich in things like lutein and other xanthophylls, may decrease the risk of developing advanced or exudative age-related macular degeneration, which is the most visually disturbing and disabling form of macular degeneration among older people. So this sat in the literature in 1994 with a call for intervention trials. This was an association study—an epidemiological retrospective—but does that really mean, for sure, that people who ate more vegetables with these pigments in them would have decreasing risk of AMD?

Over subsequent years, for nearly 20 years, clinical trials have started to appear that have been probing this particular retrospective epidemiological association. And it's those trials that I think we want to speak to, because the results look very encouraging. Now, are they hard, iron-cast, we-know-absolutely-for-sure? I would say no, but directionally we have some very good information from human intervention trials that certainly point the direction towards the relative understanding of the role that certain nutritional components play in the prevention and maybe even the management of at least earlier stages of AMD.

Let's look at some of these studies, just in preparation for our discussion with Dr. Kaushal. Recently, in the *Journal of Nutrition Health and Aging* (this is a 2013 issue, volume 17, page 219), a very interesting paper was published looking at biomarkers of oxidative stress in patients with this wet age-related macular degeneration, the most problematic form of it. The studies showed that people with this condition have an increased oxidative stress condition going on within the eye, and this is a consequence of factors that activate inflammatory processes.[4] Inflammation rears its ugly head once again, in this case with eye pathology.

What they found is that these processes are triggered by the accumulation of various advanced glycosylated end products, or what is sometimes called "AGEs." Where do these come from? They come from the connection of glucose with proteins that then damage proteins and make them into funny proteins. I call them "crusty" proteins because this is a little bit like when you bake bread. The sugar in the bread connects with the protein in the dough to then form this crust that occurs after baking, so if you think about crusty proteins in your eye that's not so good. And that can activate this oxidative injury and inflammatory effect.

Now it turns out that these ocular pigments I was speaking of, these xanthophylls that are concentrated in the fulvia of the eye, are antioxidants, and they help to protect the eye against oxidative injury. They are also photosynthetic, meaning they are photo-reducing pigments. Because the eye is always exposed to sunlight, the eye enhances its own oxidative risk just as a consequence of light exposure. You probably know that's why we recommend sunglasses if you're going to be exposed to a lot of UV radiation, because these wavelengths of light can cause damage to proteins in the eye and induce retinal damage and

changes in lens opacity that are associated with cataracts. So, here's another example of multiple effects that could enhance or increase the relative risk to the eye over time. One day or one month or even maybe one year, or over several years or several decades of cumulative injury that then accelerates and becomes more problematic and eventually leads to the diagnosis of AMD, which, in the latter stages, as I mentioned, we don't have really good treatment for, and so the person goes on to unfortunately become blind.

Personalized Approaches to AMD Prevention and Management

Can we, then, use nutrients, at some level in this process, in supplementary form, or can we change the diet through personalized lifestyle intervention, to retard or maybe even turn back this trend towards injury to the eye? That's the kind of work that's being done now and published. One of the family of nutrients that's been found for maintaining the structural integrity of the eye and resisting some of these changes that we associate with AMD are none other than our good old friends, the omega-3 fatty acids. So, you know, it's not one nutrient. It's not just, "Oh, everybody take lutein because that's going to be the savior to AMD." No, it's multiple factors that play roles, as I mentioned. If you have insulin resistance, and hyperinsulinemia, and poor glucose management, that can increase the risk. If you have photoexposure (excessively exposing your eyes to UV light), that's another risk. If you smoke, that increases oxidative chemistry in the eye, that's a risk; in fact smokers have a much higher incidence of AMD when they grow older than non-smokers. And then we talk about omega-3 fatty acid consumption. If you have a low omega-3/high omega-6 diet, which is the proinflammatory fat diet, then you have an increased risk to AMD as well. So, all of these things accumulate together. It's not just like one factor is the panacea.

In the *Journal of Nutrition* in 2013, a very interesting paper was published titled, "High Concentrations of Plasma Omega-3 Fatty Acids are Associated with Decreased Risk of Late-Age Macular Degeneration." This appeared in volume 143 on page 505.[5] Again, they did some wonderful photography of the eye, looking at the effects of omega-3 polyunsaturated fatty acids on the prevention of late-age macular degeneration, highlighting the fact that it looks like omega-3 fats are very protective. Now, again, we don't have what I would call definitive intervention trial data yet, and in fact, some of you probably know that there is a little bit of work that's been done by Cochrane; the Cochrane database did do a systematic review of the strength of data on omega-3 fatty acids and AMD, and what they say is: "Evidence from animal models is strong and observational studies in humans looks very suggestive that increased omega-3 fatty acid intake is associated with lowered risk to injury with AMD, but we are still lacking a good definitive long-term intervention trial, so they're saying it still is speculative and not completely proven.[6] But if you're evaluating options, this might be an option at least that at worst does no harm, to at least make sure that you've got proper omega-3 fatty acid intake.

Now what about the xanthophylls (these flavonoids) that are the pigments; do they play a role? Of course, here we've got some pretty good intervention trials in humans that have actually started to look at specific doses of intake, like low lutein intake (it would be something like 10 milligrams a day versus high lutein intake supplements, which are 20 milligrams a day, versus placebo), and asked: Can you increase the plasma level of these pigments? Can you increase the level in the eye of these pigments by supplementation? The answer is yes. There is a dose response, graded effect of serum levels of these

pigments and ocular levels of these pigments, and you can measure these in the eye actually non-invasively using what's called macular pigment optical density. I won't go into the technical details, but this is a way you can look into the eye with a specific measuring device and you can measure the density of these pigments in the eye. What is found is that by increasing levels in the diet, either by supplement or by food, that there is increasing concentration in the eye. Remember, I said this is the only place in your body where a pigment is intentionally concentrated selectively, for a functional aspect of your physiology. So the body knows what to grab out of your diet and to put it, in that form, in your eye. That is, if you're eating it. If you're not eating it, you can't grab it and put it there. So there is a good bit of data saying that intervention trials do show a dose response effect of lutein and also of zeaxanthine.[7] Some of you know zeaxanthine is the yellowish/golden pigment found in corn. It's the principal colored pigment in corn, whereas lutein is the principal pigment found in orange/red vegetables and in your dark green vegetables as well.

So omega-3 fatty acids and the visual pigment carotenoids/xanothophylls do appear to be very important. What about vitamin A? Because we think of vitamin A, which is produced from beta-carotene by an enzyme in the body that splits beta-carotene into two vitamin A molecules. People have started to look at vitamin A's relationship to macular degeneration, and it's interesting that vitamin A seems to have some added value to that of carotenoids themselves. Rather than being a pigment, vitamin A is not colored, but it affects the expression of certain genes. Vitamin A has a specific gene expression response effect through what is called the nuclear orphan receptor family. That's a big term, but what it means is on the nucleus of cells you have these receptors that are bound to various activating substances, one of which is retinoic acid derived from vitamin A, which is retinol. The retinoic acid receptor binding site on the surface of your nucleus of cells, like your ocular cells, is stimulated by retinoic acid (and by the way, this receptor co-hybridizes often with 1,25-dihydroxycholecalciferol, which is vitamin D3). The combination of vitamin D3 and vitamin A, as retinoic acid, on these receptors activates a family of genes that then regulate retinal health. So, vitamin A plays an important role beyond that just of beta-carotene. In fact, there are quite a few intervention trials performed under controlled conditions (in animals, I want to emphasize) showing that graded intakes of vitamin A can have a very positive effect on regulating the expression of genes that are associated with visual pigment activity. For example, rhodopsin, a protein that is involved with visual acuity in the rod cells of the retina , orphotophosphodiesterase transduction and fatty acid elongases that are all regulated by vitamin A in the retina of the eye. So again, I want to emphasize vitamin A, carotenoids, xanthophylls, omega-3 fatty acids, staying away from high glycemic load diets which stimulate too much glucose and insulin activity. In fact, there is a very interesting animal study that looked at the relationship between glycemic index and ocular health, which showed that high glycemic load diets increase the risk of what we would call the animal model for AMD.[8] So again, all these things speak together as to the importance of lifestyle in enhancing or modulating the function of the retina that then helps to prevent, in years of service—like 7 decades of living—the relative risk of AMD. Are there nice studies that have been done demonstrating intervention-positive outcomes? There's a nice study that was published in the journal Ophthalmology in 2012, volume 119, that was an intervention trial with a graded dose of lutein and zeaxanthin (10 milligrams a day of lutein, 10 milligrams a day of zeaxanthin) versus placebo showing a trend towards improved visual function and what looked like early-stage prevention of AMD.[9] Again, these are short-term trials. You really probably need a much longer-term outcome trial to fully nail this down, but you have to go off what you have, so an 8 to 12 week trial is generally the length of most of these studies at this point. There's another paper that was published in the *American Journal of Ophthalmology* in 2012 that demonstrates improvement of retinal function in early age-related macular degeneration after lutein and zeaxanthin supplementation, and this was a

randomized, double-blind, placebo-controlled trial in 108 subjects with early AMD, showing that the 10 milligram per day lutein and 10 milligram per day zeaxanthin combo was associated (versus placebo) with reducing the trend towards advancing AMD.[10]

Again, I think this field is still in a state of interesting development of more support for the association between lifestyle, diet, and AMD, but it certainly looks very, very strongly associated, particularly now that we now have started to develop a mechanistic understanding of how these pigments work as antioxidants and photo-reducing agents that prevent these oxidative injuries to the eye. There's a wonderful review paper in *Free Radical Biology in Medicine* in 2012 that talked about the mechanism by which these pigments reduce photo-oxidative injury and modulate the expression of inflammation-related genes in retinal cells.[11] As I mentioned, if we just look at the general trend of what's going on right now, if we do nothing—if we just use the available drugs that are on the market today to try to treat this—it's not looking too good. That was kind of a double entendre, wasn't it? A play on words: Not looking too good. Diabetic retinopathy and age-related macular degeneration are increasing almost exponentially in our culture. We're growing older, but we're not necessarily growing older healthily, and blindness is becoming a very, very big problem. There was a paper that was published in 2012 in the *American Journal of Preventive Medicine*, volume 43, page 48, that talks about the high frequency of unawareness among older age people of diabetic retinopathy and its relationship to age-related macular degeneration and how that relates to lifestyle habits—that older age people just do not understand this.[12] It's not been a topic of conversation. Their doctor has not discussed it with them, and so it's almost like a firestorm burning uncontrolled. And so either foods that are rich in these pigments, or supplements, have been found to be valuable. There is a paper published in the *British Journal of Nutrition* in 2012, volume 108, page 334, that compared nutrient supplements containing lutein and zeoxanthine versus consuming foods that are rich in these pigments—natural foods (it could be spinach, for instance, or carrots)—and showed that there was value in either of them (either through the supplements or through the foods that are rich in these pigments).[13] Again, I want to emphasize the data says it is a whole-body, functional effect. If you're a smoker, if you're a high alcohol consumer, if you're an individual who has a lot of proinflammatory dietary habits, you are at much higher incidence risk of AMD. And so it's a full change. It's a functional medicine, lifestyle, personalized change that really can turn the tide in the other direction, and it's that that we'll be talking about with our extraordinary clinician/researcher of the month, Dr. Kaushal, who will help take us through a better understanding of what's occurring at the forefront in this very, very important area where drugs and surgery are not the answer. It appears as if a functional medicine approach using personalized lifestyle medicine is the preemptory approach that we available today. So with that, let's turn our attention to speaking to a person in the know in this extraordinarily important area

INTERVIEW TRANSCRIPT

Clinician/Researcher of the Month

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Here we are once again—that's the moment I think you and I wonder, "Okay, who's the next exciting

person we're going to explore some visions of the future with in medicine?" Boy, are you up for a real great treat today once again. We've been so fortunate to engage in conversation with a thought leader, an expert who has quite a remarkable background, Dr. Shalesh Kaushal, who is an MD/PhD. He was an associate professor at the University of Massachusetts Medical School. Ophthalmology is—I guess you would say, his "label," although as you'll find, he is far-ranging and broader in terms of his scope of interest and impact than maybe just one medical discipline because what he's doing I think has a significant spreading effect into many other disciplines in medicine from a fundamental, heuristic, and I think didactic, and probably even philosophical perspective.

Let me tell you just a couple of things about Dr. Kaushal that I think you'll find interesting. The first point for me is some of you know I had my lineage kind of coming up through the ranks of organic chemistry and then into biochemistry and ultimately into clinical work, so he shares a little bit of an interest in that he's got a PhD with a gentleman who I had very, very high respect for back in the 60s and 70s when I was doing a lot of my doctoral and postdoctoral work, Dr. Khorana, who was known for being one of the great organic/biological interface transition people that not only was an expert in organic chemistry but he was an expert in biological chemistry and biological systems thinking. So, Dr. Kaushal did work as it relates to some of the visual pigments, which he'll be speaking more about, that enters into this whole concept of the outside environment—the photoenvironment—and interrelationship to neurology, neurochemistry, ophthalmology, and this gene/environment interaction model is obviously tied to these visual pigments.

And then of course, he has a medical degree, and is the Chairman of the Department of Ophthalmology at the University of Massachusetts School of Medicine, and has worked across many different disciplines, both as a clinician and as a researcher, and also has a very rich publication record that we're going to have a chance to talk about that relates to issues pertaining to some of the major risks that we are developing in the field of ophthalmology, like retinopathy. Some people call this a cratering—when you look at the retina of the eye of some patients they have these hemorrhagic problems and retinal injury that ultimately leads to the major cause of adult blindness in the United States, and how that interrelates with other age-related problems like macular degeneration. This concept of sight and vision is a big concern, as you know, as we start to see more and more cases of insulin resistance, hyperglycemia, and the effects of type 2 diabetes.

I think we're right on the edge of some of the most remarkable questions that will lead to solutions to these systems-related problems. It's probably not just one drug for one disease; it's more a systems approach.

Dr. Kaushal, thank you so much for being available to Functional Medicine Update, and for the remarkable opportunity to get to know you and your work. You are truly a leader in the field. I guess my first question is: "How did your path take you down into the field of ophthalmology and this bridging of gaps across the disciplines?"

SK: Yes, Jeff, thank you for having me on and taking the opportunity to share some of our thinking—my lab's thinking and my own thinking—over the years. My own educational odyssey, as it were, or training odyssey, really began at first in college as an undergraduate, where I always knew I had a passion for math and science. Actually I wanted to—at one point—be a professional basketball player (being 6'5"), but that's a rare event. But I really got turned on by a set of professors in my junior and senior year while I

was an undergraduate at Yale University, and then went on to medical school, and really in medical school I vacillated between a couple of different specialties—neurosurgery was one—and my exposure, particularly during the third-year rotations in ophthalmology with Drs. Irene and Ed Maumenee at Johns Hopkins Wilmer Eye Institute, galvanized my excitement about ophthalmology, and really the opportunity in that field (the field that I'm in) to take on a career of being a clinician scientist. Their really wonderful, strong encouragement lead me to pursue—as you've mentioned already—PhD work with Dr. Har Gobind Khorana at MIT. I was absolutely absorbed in the world of research and I actually had entertained the thought of just pursuing a postdoctoral fellowship as a scientist, but I really missed taking care of people. And that passion to combine my sincere interest in science and eventually in clinical trials as well as so-called translational research, and in simultaneously taking care of people, led me to do my clinical training first in ophthalmology and then as a retina specialist. I did my ophthalmology training out in Los Angeles at the Doheny Eye Institute at USC Medical School, and then my surgical retina and medical retina training in St. Louis at Barnes Retina Institute.

Because of that training, I felt I still wanted to spend a little bit more time learning about inherited retinal and macular diseases, and I was very fortunate to be a Fellow in London at Moorefields Eye Hospital with Professor Alan Bird and Professor Shomi Bhattacharya. Professor Bird is considered one of the international authorities in inherited retinal and macular diseases, as well as other medical retinal diseases. Dr. Bhattacharya is also a really outstanding internationally known basic scientist. It was there that I started really formulating how I might eventually pursue a career as a clinician scientist.

JB: That path, drawing from so many academic and clinical disciplines, gives you a very interesting imprint, I'm sure, on how you look at patients, how you look at their disease. I have a suspicion that it may lend itself very nicely into this systems approach that you've been developing, which we're going to talk more about. Has this been at all a challenge with some of your colleagues who don't have this broad-based perspective that you've developed over your years?

SK: Yes, there is a set of us that have been fortunate or blessed to follow this path, but from my own personal and professional perspective, once of the real beauties of being a retina specialist, or an ophthalmologist in general, is that we can actually observe the biology directly through the microscope and other non-invasive diagnostic testing that we can do (imaging that we can do) of the retina. I find it particularly satisfying, not only in terms of taking care of patients and helping them improve their vision, but also as an experimentalist, because you can directly visualize at least part of the biology of the disease. What I really enjoy is seeing patients and then trying to recast some of the biological problems related to the disease into experimentally tractable problems that can be attacked in the lab, or at least pursued in the lab, to try to better understand the disease and/or develop potential therapeutics.

JB: So with that as a basis, help us understand what's going on in disease epidemiology related to retinopathy and retinal diseases. We have these inborn diseases that remain maybe reasonably fixed, and then we've got these induced diseases which may be affected by the environment, so where are we in this whole…?

Diabetic Retinopathy Incidence is on the Rise

SK: Yes, yes. This is a great question. It's a huge concern both in terms of clinicians taking care of patients with retinal diseases, but even more broadly as a public health problem. As it turns out, for

example, diabetic retinopathy—as you are already pointing out, diabetes in general is rising essentially exponentially across the entire globe. And in addition, as you might imagine, so are the complications related to diabetes and in my own field there is clearly a worldwide shortage of retina specialists, because we simply can't manage all of the patients that need to be evaluated and/or treated for diabetic retinopathy. Likewise, macular degeneration is quickly rising to be the number one cause of blindness in the world. Right now it's the number one cause of blindness in the Western world for sure, but the incidence in the developing world is also rising quite dramatically. Between those two diseases, which is pretty remarkable in and of itself, it accounts typically for probably anywhere from 50 to 70 percent of a retina practice. In other words, the number of patients that a retina specialist will see are preponderantly patients with diabetic disease or macular degeneration. That's just those two diseases alone, and remember there are so many other retinal diseases, some as you were already hinting which have a genetic component, and others which are clearly influenced by environment, nutrition, diet, and so on that are also rising for sure. For example, certain types of vascular occlusions, you can consider them as mini strokes or strokes of the eye. The numbers of those types of patients with those types of disorders is rising as well. We're seeing a tremendous change in the patterns of referrals of patients or the incidence and prevalence of disease in a retina practice, but obviously in a larger sense in medicine as well.

JB: One of the things that I've heard people say, which I don't necessarily agree with but I'd like to get your much more well-informed opinion, is that these diseases of the eyes that we're seeing, this increased prevalence, is a consequence of the aging of our society and so this is just a natural consequence of older populations who have older eyes. Is that strictly the answer?

SK: That's a wonderful comment, Jeff, and I would say no. I don't think it's purely an aging event. We know that there is an age-related change in the metabolism of the retina and the eye in general, but the actual manifestation of disease, which is the consequence of aberrant homeostasis, as it were, in the retina, there is clear and mounting evidence of the role of environmental influences and also nutritional influences, even in our own field (or in my field) as a retina specialist, the awareness and understanding of that has begun to emerge with lovely epidemiological work done not only here in the US but elsewhere around the world. So it's clear that the profound effect of nutritional and environmental stressors, as it were, on the body in general and the eye as well, is increasing. I further say, even though I'm a retina specialist and primarily focused on addressing issues of the retina, these diseases that we see with retinal manifestations are really evidence of a systemic disequilibrium in many, many retinal diseases, and that understanding has started to emerge more clearly I would say over the last 10 to 15 years with both wonderful and epidemiological work, but also molecular and biochemical understandings of these disease processes where we see that even though we may directly visualize changes in the retina, we recognize that those types of changes are occurring elsewhere in the body as well.

JB: That leads to a very, very interesting question. You talked about the disease processes and your work has helped really to explicate and break through with new understandings of these processes at the molecular and cellular level, and I know that you've been doing quite a bit of work on signal transduction in some of these pathways that get disturbed or modified in their expression. Could you tell us a little bit about things like your heat shock protein work, and how you see signal transduction influencing these disorders?

SK: Let me step back and sort of set the stage—a conceptual framework—to understand some of this, for you listeners. So you might imagine, for example, in the rooms where we're sitting, to feel comfortable

we don't turn the temperature widely ten degrees one way or the other on the thermostat, which is essentially a rheostat. We just turn it a couple degrees one way or the other to be comfortable in the room. Now, think about a cell or a tissue that is stressed either by some environmental influence—for example, cigarette smoke, or some nutritional imbalance, or some genetic (intrinsic) change within the cell. So you can think of that cell, which was previously in equilibrium, now it's sort of off-kilter, just like a see-saw that's out of balance. And the real goal of any therapeutic agent is really to allow the cell and the tissue to re-achieve equilibrium. In other words, bring that see-saw back into balance. That's the fundamental idea around the therapeutic, as we conceive it and obviously many other folks as well.

The other piece of this framework is that if you think of the cell as having a set of multiple pathways—for the moment you can think of them as these little points—and these pathways are connected to each other with springs. So you might imagine that if you touch on one spring—you know, one particular pathway that's important for cell survival or cell functioning—that when you press on one spring, because all these other springs of these other pathways are connected, that all the other springs will also vibrate. Now, what does that mean in terms of a therapeutic? The way we think of it is instead of targeting a particular protein, what we'd like to do is target a particular pathway. For example, the heat shock protein pathway. There are other pathways that we're interested in as well. You might imagine that if you have a therapeutic agent—in other words, a small molecule or a drug—that can affect one of those pathways, because there's this intrinsic intelligence of a cell to rejigger itself back into homeostasis. If you affect one pathway rather than a single protein, now you have a chance for that cell to re-equilibrate. In other words, for that see-saw to come back into an equilibrium state, where it is straight (you know, parallel) with the ground again. The concept of these small molecules—I've nicknamed them molecular rheostats because they're just like a temperature regulators, as it were, a thermostat. The idea is, again, to affect a pathway, because it is interconnected with other cellular pathways, that this would allow the cell to reestablish homeostasis. We've become very interested, as you've pointed out, in the heat shock protein pathway, as well as the role of certain drugs called histone deacetylase inhibitors, like valproic acid, like SAHA and Vorinostat, and others, because they allow us to target a pathway and sometimes even multiple cellular pathways, rather than a single protein.

JB: This is extraordinarily interesting based on the way that functional medicine has evolved around a systems biology concept, because the way I'm interpreting what you're saying is the imbalances in only a few basic cellular processes give rise to literally thousands of different diseases depending on how they flow through that person's genotype into their phenotype.

SK: That's exactly right.

JB: And then that leads into the question: "Okay, if there are only a few of these pathways that ultimately control and regulate multiple outcomes in the phenotype, then what are the determinants for the expression of those imbalances in those pathways or those networks? How do those genes interface with the environment to give rise to the expression that we call that family of diseases? This sounds to me like a general precept in medicine that you're applying beautifully to retinal diseases, but it seems like it has a very broad-reaching implication.

SK: Yes, absolutely. Jeff, if I may recast it in my own terms, that's where I really find the approaches of functional medicine so resonant with what we think in terms of cellular therapeutics, what functional medicine thinks of in terms of overall patient well-being, For example, we know that for almost every

human disease, there are at least three or four clearly associated biological changes. One is there is oxidative stress. It seems, from my own reading and then talking to experts in many areas of medicine and science, there is clear evidence of oxidative stress in almost every human disease. Second, the role of inflammation in human disease processes. And third is the role of the immune system, which is being better appreciated across many, many diseases, including retinal diseases). And then finally the fourth is the role of cell death. At least in science, there is a great interest in apoptosis, or so-called programmed cell death, but there are other forms of cell death as well: necrosis, inflammatory cell death, and then there is something even called necroptosis, where there is inflammatory programmed cell death. So those four or five canonical principles of disease, at a cellular level or at a tissue level, I think resonate very well with the concepts of functional medicine that, Jeff, you and others have developed and are now starting to be practiced across the country and elsewhere.

JB: This is very, very exciting. So let's take this, now, to your work, which I think has been pioneering work, to look at how this construct translates into searching out for a drug that will treat a specific ocular disease. How does that then guide your research and guide maybe therapeutics as we look downstream as to how we're going to better manage this exploding prevalence of these conditions?

SK: Yes, this is at the level of experimental science, that's the real challenge of it all. Let me just, again, share with you some of the ideas we've developed. Obviously there are other folks who are thinking along similar lines as well. We're just fortunate we have a model system that Mother Nature has gifted to humans and mouse models, eyes that are easily observable and easily quantifiable in terms of what may be happening at the level of the biology of the retinal tissue. Experimentally, what we had set up and completed was to use the power of robotic screening—in other words, high-throughput screening in multiple assays. We're looking for molecules that have the properties of one, being antioxidants; two, that they are anti-inflammatory; third, they should have some ability to prevent cell death; and then fourth—like I was mentioning before—those canonical aspects of human disease—that they should have some ability to modulate the immune system. At first glance that may be a tall order if you look at it on the surface, but it turns out, quite interestingly, that nature solves many of these therapeutic problems with natural plant products and herbs as well. Many of them, as some of your listeners may be familiar, Jeff, and you may be familiar as well, are called adaptogens, and these types of natural small molecules (or "drugs" if you'd like to call them that) are produced by plants and herbs to allow them to survive in unusual climates (unusual cold or unusual heat). As it turns out, they have—very, very interestingly—these types of properties that I've just mentioned, that could be useful as therapeutics in human disease. Part of the attraction of all of this to me is because they're natural, they can be consumed either as the native plant or herb, or in some instances the natural product has been isolated. In fact, that's what we originally discovered. And as you might imagine, that since nature has developed these literally evolutionarily—over thousands and maybe even hundreds of thousands of years—that they must pass certain intrinsic biological safety tests, which turns out to be true, right? And without getting into the real nitty gritty specifics of it all, the excitement to me is that this interfaces directly with some of the concepts and approaches that functional medicine takes. In other words, using natural products, or if you want to recast it a slightly different way, one might imagine having these versatile small molecules that affect potentially—as I mention—multiple pathways, and thereby mitigating multiple aspects of disease manifestation, or, Jeff, as you were describing, the phenotype. This approach, to me, is conceptually very satisfying and we believe it may be the future of therapeutics in the not-so-distant-future.

What I want to point out is how it contrasts with typical approaches in academia and the pharmaceutical

industry. Typically, what happens is a target protein is identified to participate in some aspect of the disease process, and the idea is to develop a biological agent—it could be an antibody or a small molecule (a drug)—that binds to the target with extremely high affinity. Often the idea is to have something with nanomolar binding affinity for that protein target. Basically, you load up the cell, or the human being, with that drug in order to affect or change the cadence of the disease pattern. What we're suggesting is slightly different, and that is, first of all, that you don't need large concentrations of the drug, and thereby you limit the potential toxicity. And then secondly—and more importantly, as I've said before but repeat again—is the idea that you're rejiggering the cell into homeostasis by affecting a pathway or other multiple pathways within the cell that allow it to then re-equilibrate or reacquire homeostasis.

JB: I think this is an unbelievably interesting merging of what I guess some people would call traditional medical thinking from both traditional Chinese medicine and Ayurvedic medicine. It's a very powerful mixing of models into a systems biology model that addresses pleiotropy, it addresses redundancy, it addresses complexity, and it's less involved with single hits of single targets as it is modulating systems of disturbed function, so it's a really powerful concept. In your models of retinal disease have you had any successes?

SK: Yes, Jeff. We've been very fortunate to literally take things from cell culture, animal models, into humans. In fact, I've been very fortunate to present some of this work at national and international retina meetings. The first time I presented it a couple of years ago there was less interest, and then as you know, as there is more use and also additional work that is done in the area, there is greater interest and also greater scientific validation of the approach. My colleagues are now starting to use the therapeutics (or at least one therapeutic) we've identified, and we're obviously keen to replicate that. So at least we have one proof of concept and now we're seeking others—some natural products—to bring those to clinical use in retinal diseases and see that they also literally allow us to go from bench (again, from cell culture and animal models) into humans to affect the disease process itself.

The other very tantalizing idea or possibility, and I think, Jeff, you already hinted at it earlier, is in part because these disease pathogenetic events are conserved by Mother Nature. In other words, when a cell or tissue—whatever it may be: heart, lung, liver, brain, eye, bone marrow, muscle—when that cell is stressed by environmental or genetic factors, Mother Nature only has a constrained set of options from which she tries to deal with that disease. And if it isn't able to deal with that stressor, then that becomes manifest as a disease of, for example, the muscle, or the heart, the lungs, or liver. One might imagine these types of molecular rheostats…not only have we used the retina as a platform for discovery, but also they have potential utility in other diseases. Is that true? Well, at least in the mouse models we've explored of non-retinal diseases, like of the lung, of the pancreas (like diabetes), and also heart disease. Those same sets of molecules that are modulating and affecting retinal diseases, at least in our mouse model appear to be effective in these other diseases. And that would be consistent with our thinking of how a molecular rheostat should work.

JB: Yes, I'm thinking of a compound like resveratrol, which has received a tremendous amount of attention over the last decade, which we know is a histone deacetylase modulator and has effects on the sirtuin gene families and the mammalian target of rapamycin (or mTOR), that would be kind of a candidate that we might think of, from peanut skins or from grape skins that could be such a candidate for this model that you're describing.

SK: Absolutely. In fact, maybe it was rather telepathic of you, but that is one of the molecules—we haven't published that work yet, we've presented it as a poster—but we've identified it as a compound that clearly affects the cells of the retina in terms of protecting them.

JB: This is taking my reading of some of your publications to maybe a level of abstraction so I apologize if I'm leaping too far, but I'm very interested in your work on Leiber's optic neuropathy, because that's a constituent of mitochondrial deletion disorder that's genetically inherited through the maternal linkage, but it also has a very interesting model to bioenergetics and how that interrelates Leiber's optic neuropathy to myopathies and to encephalopathies because these conditions kind of come in groups of families, to talk about your multi-target types of tissues. Have you had any experience in you molecular rheostat model looking at something that's as constitutively intrinsic as Leiber's optic neuropathy, which is a mitochondropathy?

SK: Right, I think you're thinking of our published work on Leiber's congenital amarosis. That's where we've had some degree of success with gene therapy, and that's a disorder of the retina which affects photoreceptor function. But your thinking about Leiber's optic neuropathy is correct in that it is a mitochondrial disorder. I don't have direct experience with that disorder.

JB: The reason I'm asking the question is it strikes me, from the extraordinary work you've done—the systems biology approach—that this may interface ultimately at a mechanistic level with bioenergetics at the mitochondrial level.

Systems Biology and the Future of Retinal Therapeutics

SK: Absolutely, Jeff. That's a true statement for sure. In fact, in the midst of writing a prospectus on the future of retinal therapeutics, which also has implications, obviously, for other areas as well, but this whole concept of cellular homeostasis, which requires a systems biological approach to really embrace not only the complexity and nuance of disease, but also by embracing that complexity one can think about therapeutics like molecular rheostats. And again, I wouldn't say that that's the one approach, the one we're taking; there may be other approaches as well. Coming back to your comment, it has to embrace the importance of energy metabolism, because in nearly every single disease process—at least in my own reading of the literature—there are clearly effects on the dysregulation of energy metabolism. In other words, the efficiency with which a cell may produce ATP, or the way that the cell may process or use that ATP in various energetic or biological machines that exist in the cell.

JB: Let me, if I can, talk about one last area that I know you have much more depth of understanding than I, but I think it interrelates with everything you're talking about, and that's macular degeneration and its relationship to visual pigments in the fulvia, this lutein connection to diet. People are trying to understand these photo desensitizers, which are these pigments that are concentrated in the tissue and are unusual in that the body picks a certain chromaphore to concentrate. Could you tell us a little bit about how that fits into this model of molecular rheostats because it seems like it's another example of your concept.

SK: Yes, Jeff, that's right. Macular degeneration, just in terms of a little bit of clinical medicine, is quite common in the Western world; it's the number one cause of blindness in the West and it's rising throughout the world. It comes in two basic forms. I think "forms" may be a less correct term. It comes on a spectrum of disease. You can think of it almost like an autism spectrum. There's a so-called dry

form, or non-exudative form, where there is an absence of abnormal new blood vessels that are growing underneath the retina, and then there is the so-call wet, or the exudative form, where there are examples where patients develop neoangiogenesis—new blood vessels that are growing within or underneath the retina. In that disease it is clear that there are multiple, critical, pathogenetic events that occur in that disease. Some of them I've already mentioned in the general context of human disease, but we know that, again, oxidative stress, clearly inflammation, and in the case of the eyes, photo oxidative stress—in other words, excessive light exposure—we know that there is also evidence of immune dysregulation that occurs in the retina and in the body that can participate in the disease process, to name at least a few of the critical pathogenetic events. The whole idea of molecular rheostats, frankly, was born out of trying to understand or embrace the complexity of the disease itself and some of the beautiful biology that has been understood by many groups around the world as well as our own group, in the context of this disease. And so this whole concept of molecular rheostat, I think, really was born out of trying to understand how one could potentially treat macular degeneration, and we've identified a set of natural compounds, and in fact also FDA-approved drugs like some of the histone deacetylase inhibitors that you were mentioning earlier, and heat shock inducers as well, which we believe could be used to help treat this systemic disease with eye manifestation.

JB: I can tell you that I know we have just touched the tip of the iceberg with this discussion. The depth of your understanding and the way that you're using these conditions of the eye to explore and probe a general thought about the origin of chronic degenerative diseases is absolutely, to me, at the forefront of moving from a pathology-based form of medicine to a mechanistic form of medicine. I want to thank you so much, both for your work and the way you describe it and for your advocacy. I know that this must be a very exciting time for you, but it probably is also very challenging because you're trying to help people to understand—guide them to understand—this new model, which is kind of different than the model that many of us learn which was a memorization model of histopathology, and cytology, and histology, and now we're really talking about mechanisms that underlie the appearance of these conditions that ultimately fan out to be thousands of diseases in our DRG book. I really want to applaud what you're doing. I think every listener of this discussion with you has come away saying, "Wow, no matter where we look in the body, if you look at the expert who understands the mechanisms of disease, they all tend to converge on a single model, which is very, very exciting."

SK: Yes, yes, I think so. Again, Jeff, I'd like to thank you giving me the opportunity to share with you some of the ideas that have been percolating in our thinking over the last 3 to 5 years.

JB: I'm looking forward for the opportunity to have a chance to meet you at the upcoming functional medicine annual international conference. I'm sure that you're going to infect the IFM population with a lot of great new thoughts and bring this concept of eye-related diseases much more into the forefront of the thinking within the functional medicine community. Thank you so, so much, Dr. Kaushal, for sharing all this with us today.

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