Speaker 1:

Welcome to the Eye on the Cure Podcast, the podcast about winning the fight against retinal disease from the Foundation Fighting Blindness.

Ben Shaberman:

Welcome to the Eye on the Cure Podcast. I'm your host, Ben Shaberman, with the Foundation Fighting Blindness, and I'm delighted to welcome my first guest of 2023, Dr. Paul Bernstein. And Dr. Bernstein is an MD-PhD. He's a clinical researcher from the Moran Eye Center at the University of Utah where he's been a faculty member since 1995. So welcome to the podcast, Paul.

Dr. Paul Bernstein:

Thank you very much, Ben. Glad to be here.

Ben Shaberman:

Great to have you. And I'm going to read a little more about Paul before we get started with our conversation. He has some great credentials. He holds the Val A. and Edith D. Green Presidential Endowed Chair in Ophthalmology and Visual Sciences and is Moran's Director of Clinical Research and Associate Director of Research. He also has adjunct appointments in the Department of Pharmacology and Toxicology, the Department of Neurobiology and Anatomy, and the Division of Neurosciences. Paul did his undergraduate work, his MD and PhD at Harvard, and he's offered more than 200 peer reviewed articles.

Now, Paul has received numerous awards including the 2020 Mildred Weisenfeld Award from the Association for Research and Vision and Ophthalmology, also known as ARVO. And at the end of our discussion, I want to come back to that award lecture and some interesting facts about Paul to discuss then.

But one of the reasons I'm excited to have Paul on the podcast, one of his key areas of research is nutrition. And before we get into that, Paul, can you explain what your role is at the University of Utah and how it's evolved over time, because you're doing so much these days.

Dr. Paul Bernstein:

So, Ben, I came here, as you said, in 1995. I was fresh out of my fellowship at Mass Eye and Ear, and I trained, as we'll discuss a little bit more today, as a clinician scientist. And so I have both an MD and a PhD degree. And I had finished my training and wanted to find a research and clinical faculty position where I could do both, see patients and use the full value of all of my retina training that I had achieved through the years and continue to do research and in my areas of nutrition in the eye and inherited retina diseases. So I was attracted to University of Utah and came here because I had a chairman and an opportunity that really gave me the ability to try to do everything, to do it all. And when I was brought out here, they had a specific need for inherited retina diseases.

And I came out here with the idea that I would be the inherited retina disease person for the University of Utah and the Moran Eye Center. And it turns out I've been very, very busy, and I am the main person who sees inherited retina diseases for the entire Intermountain West of the United States. So although I probably have, I don't necessarily have the largest practice in terms of population for the United States, I probably have the largest practice in terms of geographic area. So I see inherited retina disease patients from Utah, Montana, Wyoming, Idaho. And I'm talking about the whole state, covering... Essentially, I'm

the only inherited retina disease person here. And I also cover Western Colorado and eastern Nevada too. So it's a lot of area here.

My role here is to see inherited retina disease patients, to run a research laboratory, and to do other retina things. I'm trained surgically, and I still do surgical retina. So I see diabetic patients. I see age-related macular degeneration, and I am very busy. Sometimes I say... People ask how I divide my time. Well, I'm 50% clinical, 50% research, and 50% administrative. 'Cause I've actually been promoted to vice chair for research for the department. So if you can add, that adds up to 150% time, and that's really true. So it's a very busy time here.

Ben Shaberman:

Well, we greatly appreciate you dedicating 150% of your time to our space. Inherited retinal diseases are a challenging career path. A lot of doctors don't jump into it. So we really appreciate the fact that you put so much focus on it both in caring patients and doing some great research. So what inspired you to get into the eye, the retina, and specifically IRDs? How did you get started?

Dr. Paul Bernstein:

So I come from a medical family, and I was very interested in research as well. And as an undergraduate, I studied organic chemistry, which is the bane of many people who go into medicine. But I loved it and really liked the chemistry and really working in the laboratory and synthesizing chemicals and new drugs. And when I went to medical school to get my MD-PhD, I had to find a research laboratory of something that I wanted to do. Now, I would say at that time, besides seeing eye doctors for my glasses, I had no other specific reason why I would be interested in the eye. But when I was looking for research laboratories, I wanted to work for the best chemist I could find. And so I approached Dr. Robert Rando back then in the 1980s and said I was interested in doing chemistry-type work that would have medical applications and wanted to learn about various projects that he was working on.

And he gave me a project that was on vitamin A metabolism in the eye. Vitamin A is a chemical compound. It's a retinoid. And I learned about this, and I learned about the mysteries of what we knew about vitamin A and how it could help, say, for night blindness and things like that and perhaps even inherited retina diseases. But the project that I was put on was to try to figure out how vitamin A was made into its active form called 11-cis-retinal and 11-cis-retinol. And my goal was to figure out how this is being made, because this active form of vitamin A binds 2 opsin and makes rhodopsin, the fundamental protein that we all require for vision. And I worked on that project. I figured out that there really is an enzyme in the eye and how it would work. We couldn't identify it, actually, the protein back then because the molecular biology wasn't quite good enough in the 1980s to figure that out.

But I could figure out that this was going to be a very, very important enzyme in the eye and that it could even have important, it may be important in terms of inherited retina diseases. My work got published, and I realized that eye research was a great field to combine being both a researcher and clinical science. And I had learned a lot about the eye, and I realized that I wanted to be very focused on what I did, but to also have long-term impact on patients and long-term relationships. And so I decided to stay in ophthalmology and get my training and continue on through this. Now, the protein, the enzyme that I discovered eventually turned out to be RPE65. And that led to the first gene therapy. So even back 30, 40 years before we actually found our first gene therapy for eye diseases, I was at the ground floor of trying to figure some of these, figuring out the biochemistry that we needed to know.

And it's been a great field. I've really been very, very happy that I chose this field. It's been very rewarding because there's so many people we can help if I fix retina detachments, if I can fix diabetic

retinopathy. But I also realized that there's a huge need for patients where the diseases were not so simple to solve, were not, I wouldn't say, or were not so straightforward, let's say that. And so that attracted me to be working with inherited retina diseases and with age-related macular degeneration, which was, especially back then had no treatments either. And so many, many patients were going blind. But I found that I could, that there were enough, very interesting research problems, very interesting approaches.

I really liked the idea of focusing on nutrition in the eye because in many different ways patients were very motivated when they have difficult eye diseases to ask what can they do that empowers them to really start to tackle some of their eye problems. And, of course, nutrition is one of the things that all of us can really probably improve. And eye disease has turned out to be a great focus for that.

Ben Shaberman:

Well, thanks for sharing that story and your entry into the retinal world. I've known you for a long time. I didn't realize that your early research was in the visual cycle, the metabolism of vitamin A. That's really cool. So let's talk about nutrition a little bit because that's what I consider to be your real wheelhouse. When I have questions about nutrition for retinal disease, you're the first person I reached out to.

So with nutrition, like you just said, the nice thing is we all can do it. We can get supplements. Most of them are over the counter. They're accessible. They're relatively safe in most cases. But nutrition is also, I think, a challenging area of research for retinal diseases. Can you talk about what the challenges are for trying to figure out if a nutritional therapy or a supplement is working?

Dr. Paul Bernstein:

Yes. I think the nutrition I've found in, for my research, it still has to be very grounded in good, basic science and good clinical research. And one of the challenges is that nutrition is, on the other hand, very accessible to patients. And so there's a lot of people that consider themselves experts out there that don't always go with the science. So that's one of the challenges is to make sure that we have good science, that we're combating misinformation. But on the other hand, for those of us on the front lines, we have to be very open to what our patients are telling us, what things are working for them to try to understand that there isn't always good, basic science to support everything that people are doing for nutrition. And so there are things that we have learned through the years that come from, say, Chinese traditional medicine where there really is very good reason why certain nutrients were selected through the years as being healthy for the eye.

And if we can understand the biochemistry, we may learn and get good evidence-based recommendations. The other challenge, of course, is that some people embrace nutrition probably a bit too much, where a good amount is healthy for the eye, so they think, well, I can take even more and more. And sometimes too much can be a problem. Some of the nutrients that we ingest might cause crystals in the eye, could cause even unintended consequences. So that's a problem.

Finally, I've learned through the years to have really great respect for the nutrition field and how difficult it really is, especially in clinical nutrition, because we all eat our varying diets, and it's very difficult to quantify sometimes what of the many nutrients we consume can be quantified to understand how much we're intaking, how much it's really influencing eye diseases. So that's where the very large scale, they were some of the original big data people 30, 40 years ago looking at doing nutritional surveys on hundreds of people trying to understand and give us leads on what we should be studying in terms of nutrition. So they are really helping us go forward.

But then to finally decide to make recommendations to our specific patients, we have to do very large clinical studies. I think we're going to talk about the original vitamin A studies by Dr. Eliot Berson where the resources have to be devoted, whether by the government or by foundations like the Foundation Fighting Blindness to actually do the trials and give good evidence-based recommendations so that we're guiding people in the proper way, in a safe manner.

Ben Shaberman:

Certainly. And would you agree that a good nutritional study might take several years because often with nutrition you're slowing disease, and it can take a number of years to actually capture the efficacy?

Dr. Paul Bernstein:

Yes. That is true. We have to be patient, and we have to give adequate resources. The other thing that we have to be very careful is the balance between recommending supplements versus natural diets, our holistic, going the more holistic approach. And I live in the area here in Utah, which is the nutritional supplement capital of the United States and maybe even the world. So patients here are very interested in nutritional supplements, but I have to sometimes tell patients, "Take a step back, have a healthy diet as well, that a pill doesn't solve everything." But on the other hand, in certain situations where people cannot change their diet or cannot consume as much as we would like them to consume of a certain nutrient, that supplements can be very important as well.

Ben Shaberman:

Right. I didn't realize Utah, your region was the capital of supplements and nutritional things. That's interesting.

So when I first started with the foundation, I remember I listened to Alan Ladees give a presentation on nutrition, and in addition to talking about the things that are good for your eyes, he mentioned that people should avoid junk food, bakery and cookies with trans fats and those unhealthy ingredients. Do you agree with that?

Dr. Paul Bernstein:

I do to an extent, yeah. I think that nutrition for both, for eye health and for health in general, I would say most people agree that the American diet is a big problem, that we don't consume enough fruits, whole fruits and vegetables is probably the number one thing that we really need to consume. The junk food that we consume, we consume too many carbs, probably too much red meat and saturated fats. So all of those are things that we should be improving in our diet. We know that obesity is a big problem in the United States, that diabetes is getting worse. So all of these things are important to do. And so I do counsel my patients almost as that is the first line of things to be approaching for the eyes.

Ben Shaberman:

Right. So recognizing that inherited retinal diseases, for example, a condition like RP can be very genetically diverse. In other words, there are a lot of different forms of RP, makes the condition or the family of conditions kind of a challenging target. What are the general recommendations you make to patients who have what we call the outer retinal conditions like RP, choroideremia, Usher syndrome, where the condition starts in rods and eventually affects cones? Are there some general guidelines that you give your patients?

Dr. Paul Bernstein:

Sure. So I talk to them about diet. I talk to them that for all of these outer retinal diseases that having healthy photoreceptors is the things that we want. Even if there is a genetic defect that's affecting either the rods or the cones out there, that it's important to consume green, leafy vegetables, dark orange and yellow fruits and vegetables and cold water fish. Now, what do they all have in common? Well, they all have, are high in nutrients that are naturally concentrated in the eye. So the green, leafy vegetables are very high in lutein. That's concentrated in the photoreceptors, especially in the macula, but even in the peripheral retina. Colorful fruits and vegetables often have the zeaxanthin, which is another carotenoid compound that's concentrated in the eye. And then the fish are very high in omega-3 fatty acids and they are fundamental to making the membranes of the photoreceptors.

So I've always found in my principles of nutritional biochemistry that if the eye goes out of its way to actually accumulate a nutrient, there's got to be a good reason that it's there, and that's probably healthy, and we need to understand how it's working, and we need to consider them for supplements. The same would be true for vitamin A compounds. The work that I did in my, originally, we need vitamin A for vision. But vitamin A is an excellent example where if you take too much preformed vitamin A, it can be toxic, and it actually can be damaging to the retina, it can be damaging to the rest of the body. So there is a balance of what we do. But so much that we've learned through nutritional epidemiology has shown that these fruits and vegetables and the fish are consistently associated with good health of the eye.

And when we talk about people with inherited retina eye diseases, things have changed dramatically in the last 30 years. We can genotype people and understand at a molecular level what is their particular problem. When I first came into this field, we didn't have any of that. We just had people with RP, and we did the best that we could with nutritional recommendations. But we've now learned that there are various forms of RP that where vitamin A would be detrimental. And same would be true for Stargardt disease. But there are other times where there are defects in vitamin A metabolism and taking more, increasing the vitamin A level could be good. So that's why now rather than a one size fits all, especially with regard to supplements that could be toxic, it's very important, and I know the Foundation Fighting Blindness is definitely behind this, for patients with inherited retina diseases to be genotyped. That way we can understand what is going on, what is wrong with their eyes, and to make sure that we get the right potentially customized treatment for them that will get them the most benefit.

Ben Shaberman:

Those are great points, great points. And RP alone, you have somewhere in the neighborhood of 80 to a hundred genes, each of which when mutated can cause the disease. And it's really in a way like 80 to a hundred different conditions, and the mutated genes affect the retina in such different ways. So I think that's really important to underscore, and for people, especially if they're interested in taking the vitamin A regimen, Dr. Berson's vitamin A palmatate, DHA lutein regimen, we do have a guidebook or a handout on our website that outlines how one goes about taking that regimen, but it really should be done under the supervision of a doctor and preferably a doctor who understands inherited retinal diseases. Would you agree with that?

Dr. Paul Bernstein:

Yes, I definitely do because people need the need to be talking to physicians who are interested in their particular condition because these are not simple conditions and to really think about it and think about what we know in terms of their clinical condition and their genetic profile, what would really be working well for them.

Ben Shaberman:

Right. And if people listening have questions, you can reach out to info@fightingblindness.org. We can try to answer the questions, or we can send you to somebody, a good clinician who has a good understanding of the conditions and nutrition.

So another point that you touched on that I think is really important and that is vitamin A being harmful or detrimental to people with certain inherited retinal diseases, namely Stargardt disease. And can you talk about why that's the case?

Dr. Paul Bernstein:

Yes. So classic autosomal recessive, recessive Stargardt disease, which is also known as STGD1, or Stargardt 1, is a disease where there's a mutation in the ABCA4 gene, and that gene is involved in moving vitamin A within the cell and helping it move from cell to cell. This is a very important part of the visual cycle. This is what I studied for my PhD in the 1980s where the rhodopsin, when it absorbs light, it releases its 11-cis-retinal chromo 4 goes to the all-trans form and then has to be released from the protein and then shuttled to the retinal pigment epithelium, which are cells that are just adjacent to the photoreceptors, where they're essentially reprocessed into the active form and returned. That's the visual cycle. We're all familiar with this. It does take time for this to happen.

That's why when we go from a bright room to a dark room, it takes us a few minutes, even all of us, a few minutes to adapt and to essentially recharge our vitamin A. If someone has a problem in this particular gene called ABCA4, the vitamin A compounds hang around too long in the photoreceptor. They don't get moved on to their next step. And once that happens, they start interacting, they're chemically active, and they start interacting with other fats in the eye, lipids called phosphatidylethanolamine, and they start to make a number of toxic compounds that we commonly refer to as A2E that accumulate in the eye and we think contribute to the degeneration that occurs in Stargardt disease.

If someone consumes a lot of vitamin A or too much vitamin A, you would get even more backup of this system and more of these toxic compounds accumulating. So we recommend that patients with Stargardt disease do not take vitamin A supplements. They don't have to go on a totally vitamin A restricted diet, but they should not be overdoing the supplements because it would work against them. Now, there are some less common forms of cone-rod dystrophy that look like RP and that don't look like Stargardt disease that are actually ABCA4 diseases. And if that happens and if we identify that, those patients should definitely not be taking vitamin A supplements as well.

Ben Shaberman:

Right. Great points. And would you say if a person is not sure what the retinal disease is, and this happens, sometimes even excellent clinicians have a hard time diagnosing patients with a specific disease, but if somebody doesn't know exactly what disease they have and they don't know what the mutated gene is, would you say they should avoid taking Vitamin A just in case it's a form that would not benefit and actually be harmed by vitamin A?

Dr. Paul Bernstein:

Yes, to an extent. I would not recommend the high doses that were originally studied by Dr. Berson, the 15,000 units a day, without being genotyped, without having their genetics checked and without having an inherited retina disease specialist that's really confident that this is not going to be a case where it would be harmful. So that's kind of where I'm at right now for my recommendations. And, of course,

very high doses of vitamin A can cause other problems. They can cause liver problems. They can cause high pressure around the brain. So these are technically supplements, but we have to treat them, at high doses, they can be drugs as well.

Ben Shaberman:

Right. And especially the 15,000 international units, that's a pretty high dose and you need to be-

Dr. Paul Bernstein:

But on the other hand, I don't think patients have to be totally paranoid about any vitamin A supplements, because some supplements have three to 5,000 international units. That's not that different from what we consume in the diet. Plus, not all vitamin A is created the same. There's vitamin A palmitate, retinal palmitate, which is preformed and ready to go to be used, and that has some potential toxicity problems. But, actually, most vitamin As that we get in our supplements is actually beta-carotene or similar provitamin A compounds. And those are not nearly as worrisome because in of themselves they're not particularly toxic. Although even high doses of beta-carotene, if you're a smoker, can lead to lung cancer. That's another example of where more is not always better. But the body has its own regulatory pathway that if we don't need any more vitamin A, the beta-carotene is just stored away and gives us a little bit of a yellowish color to our skin. So it's not quite so bad. And some people actually like it.

Ben Shaberman:

It looks like you have a suntan. Right?

Dr. Paul Bernstein:

That's right. Yep.

Ben Shaberman:

That's great. Well, thank you for that great overview of vitamin A and nutrition. It's an important field and an important way to try to help manage your condition. But it's nuanced. It's challenging. So we appreciate you sharing your perspective, which comes from many years of research and experience.

But my last question or the last thing I wanted to talk about actually ties back to the Weisenfeld award that you won a couple years ago at the ARVO research meeting. And I was in the audience, and I was all excited to hear you give your lecture, and they gave a really nice introduction to you. They talked about your hobbies and your interests, and one thing I thought was really cool is that you collect trees. Yes, trees. And I had never heard of somebody doing that. So can you tell us about your tree collection?

Dr. Paul Bernstein:

Sure. When I was growing up, my best friend became a landscape architect. But we, together, learned about trees, and I've found it to be a fascinating field. Probably one of the reasons why I've gotten into nutrition is my interest in plants. And through the years, I've become my own kind of amateur landscape architect. Even though I don't have a lot of land here, I've collected some very rare trees. My specialty are conifers, so these are trees that generally don't lose their needles. These are the pines, but I don't... pines and spruces, but I go for very unusual trees, Cyprus, things that are in the araucaria family. And although we don't have a, this is not a video podcast. And so I was telling Ben in the background, I have a bunya bunya tree in my office, which is a tree from Australia that's very spiky and very unusual.

And I collect other ones in that family, including a Wollemi Pine, which is from Australia, one of its relatives that was only discovered in 1993 in a small forest there. And I have one of those in my greenhouse at home. I love to have people come over to my house, and I can give them a complete tree tour of all these unusual trees. I pick them for their color, their size, and their shape, and it makes it hard. That's one reason why I've never moved from my house in 27 years. 'Cause if I move, I'm going to be selling off my tree collection. And so it's been a fantastic hobby, and it's one that's lifelong.

In fact, although it's not technically a tree, the other thing that I'm very proud of is I have the original plant that I bought in second grade, a grocery store cactus. I still have that one to this day. It's now getting up to late 50, almost 60 years old. I've moved that around with me everywhere that I go, and it's part of our greenhouse, and it's been a great hobby. And it's actually how I met my wife, too, because she's into plants herself. So we feed upon each of our interests.

Ben Shaberman:

That is so cool. I didn't realize that that's how you met your wife. That that's such a great story. Plants and love and it's keeping you in Utah too.

Dr. Paul Bernstein:

Yes.

Ben Shaberman:

Which is real nice. I'm sure the University of Utah appreciates your tree collection 'cause it makes it harder for you to venture off to another institution.

Dr. Paul Bernstein:

Yeah, my latest one that I added is a monkey puzzle tree, which is, again, a relative of my bunya bunya tree. But instead of from Australia, it's from Chile, and I'm growing it outdoors. I think I have one of the only ones that's been successfully grown outdoors here in Utah.

Ben Shaberman:

Wow. That is so cool. So can you describe what a monkey puzzle tree might look like or what it does look like?

Dr. Paul Bernstein:

Yes. It looks almost prehistoric. It's got big spiky needles, and so why it's called a monkey puzzle is that its needles grow on the trunk as well. So monkeys have a hard time figuring out how to climb it, apparently, in Chile

Ben Shaberman:

It sounds like a painful climb-

Dr. Paul Bernstein:

Yes.

Ben Shaberman:

-if a monkey were to attempt that. Well, Paul, this has been a really informative discussion. I've known you for a long time. I've heard you talk. I had a lot of discussions with you, but as always, I've learned a lot from these conversations. So thank you. I appreciate you sharing part of your day to talk about nutrition and trees, and we wish you the best of luck in your research. We really haven't had much of a chance to talk about your research, but perhaps later in the year we can have you back to talk about some of the research projects you're working on. That would be informative as well. So thank you Paul for joining Eye on the Cure. And thank you to all our listeners. We appreciate you tuning in, and we'll have a new episode in a couple of weeks.

Speaker 1:

This has been Eye on the Cure. To help us win the fight, please donate at foundationfightingblindness.org.