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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 very excited to have as my guest for this episode, Dr. Jason Commander. He's a retinal disease clinical researcher and director of the Inherited Retinal Disorder Service at Mass Eye and Ear, which is part of Harvard Medical School. Jason, welcome to the podcast. It's great to have you.

Dr. Jason Commander:

It's great to be here. Thank you for inviting me, and I've been looking forward to this.

Ben Shaberman:

Well, we are excited to have you talk about your career and some very exciting research that you recently concluded. And we are going to spend much of the podcast discussing the work that Dr. Pierce and Jason did in re-analyzing patient data from Dr. Eliot Berson's original, well-known clinical trial for vitamin A supplementation therapy for retinitis pigmentosa. That study was conducted about four decades ago and has been the subject of much discussion and controversy in the retinal research community.

But I would be remiss if we didn't take a moment to talk about Jason's impressive background and important contributions to retinal disease research and patient care in other areas. So Jason earned his MD and PhD from Harvard Medical School and he completed a Harvard ophthalmology residency, a vitriol retinal surgery fellowship, and inherited retinal disease training at Mass Eye and Ear. And in his early clinical career, he was the recipient of a career development award from the Foundation Fighting Blindness.

We're very proud of the work he did in receiving that award. And while Jason has also led genetics related research efforts in the lab, what's most impressive to me is his role as surgeon and lead investigator in several clinical trials. In fact, Jason and his team performed the first procedure for an FDA approved gene therapy for any inherited disease, and that was in 2018, and the gene therapy was Luxturna, which has restored significant vision to hundreds of people with RPE65 mutations around the world.

And also in 2020, Jason and the Mass Eye and Ear team performed one of the first gene editing surgeries to deliver a CRISPR-Cas9 gene editing therapy directly to the human body or as the experts like to say, in vivo. So Jason, let's start at your beginning. I had like to hear about where you grew up and what was fun for you as a kid. Were you really into science at a young age? And what led you to get into science and clinical care?

Dr. Jason Commander:

First of all, thank you for that very kind introduction. I get embarrassed easily, and I just need to point out that a lot of those accomplishments that you mentioned, I was part of big teams of people. Luxturna, people at Penn and elsewhere around the world have been working on that for 30 years. So I try not to take too much credit for any one thing, but I really appreciate the intro very much.

As you might expect for someone who's gotten into medical research and science, I was indeed interested in techie things when I was a kid. I had a bin of things in my bedroom. And when anything

electronic broke in my house, I would put it in the bin and I would take it apart and try to figure out how it works. And it was only when I got a little bit older that I was able to start putting things back together again.

My favorite course and college was electronics and I loved tinkering with gadgets and things. And I think that a part of my job where I get to play with gadgets and do technical things, it's amazing. It's part of my salary to do this fun stuff. So from a young age, that was my affinity.

Ben Shaberman:

But that translated into biology really and the eye. So can you talk about at what point in your career you decided to move into biological sciences and specifically the eye?

Dr. Jason Commander:

Yeah, it's kind of one of those coincidences. When I was 16, I saw CNN Biomedical Engineering Special. And like every 16-year-old I was trying to figure out what I wanted to do, and I said to my mom, "Oh, that biomedical engineering, that looks interesting." And she said, "Oh, one of our family friends did a fellowship in a biomedical engineering lab at Bascom Palmer Eye Institute in Miami. Maybe we can get you a tour." And I got a tour and I managed to talk it into a part-time job.

This was when I was a teenager, and I started in the basement sorting screws and doing all kinds of things. And eventually I worked my way up out of the basement into doing some data analysis and mathematical projects. And I had a really great, kind mentor, Jean-Marie Parel. He was a great man, and he had faith in me and took me under his wing. And before I knew it, I was 17 years old doing an oral presentation at ARVO on the temperature distribution of the cornea.

And that was my start into ophthalmic research when I was a teenager. And I tried other things along the way, like I did some cardiology research for my PhD, but nothing is more interesting than the I and I just kept coming back to it. And here I am.

Ben Shaberman:

And you mentioned this mentor, can you say his name again and where he was at?

Dr. Jason Commander:

Sure. Jean-Marie Parel is a biomedical engineer who runs the lab at Bascom Palmer Eye Institute.

Ben Shaberman:

Got it. That's really cool that you really got hooked into our space even before college.

Dr. Jason Commander:

I was very fortunate. It certainly did help me get into college. I appreciate.

Ben Shaberman:

I'm sure. I wonder if I saw your... What year was your ARVO poster when you were 17? Can I ask?

Dr. Jason Commander:

It must have been 1991 or something like that.

Ben Shaberman:

Oh, okay, okay. That was before my time at the foundation. Interesting. So you moved into the ophthalmology space. And in reading your credentials and doing research, you've done just about all of your education and residency fellowships, et cetera, at Mass Eye and Ear. What drew you to Harvard and Mass Eye and Ear?

Dr. Jason Commander:

Well, it didn't mean for it to happen that way. It's all Harvard affiliated training. But at every turn, it was the best opportunity. If you want to do good work, the most important thing is to be around good people who can teach you and you have to work up to their level. And here I am and here I stay and I couldn't be happier. It's really a privilege to work here specifically at Mass Eye and Ear in inherited retinal diseases.

Ben Shaberman:

Right, and we're delighted to have you at Mass Eye and Ear. And for our listeners who don't know, Mass Eye and Ear was the first research center that the foundation funded just after the foundation was established in the early '70s. So you really started at the top.

Dr. Jason Commander:

Yeah. The history is really interesting to me and really important. Every morning when I walk into work, I pass by the sign in the hallway that says The Berman-Gund Laboratory for the Study of Retinal Degenerations founded in 1974 with support from the Retinitis Pigmentosa Foundation. It was this little organization, like you said, founded in 1971, which in the '80s and '90s got renamed to the Foundation Fighting Blindness.

And here we are now, look at all that FFB does. Because of that early support here, we have this decades long history of inherited retinal disease and RP research. And I'm sure we're going to get into the details of that real soon.

Ben Shaberman:

We are. But one question before we start talking about the vitamin A study. So you do retinal surgery and I'm always odd and amazed by doctors who do retinal surgery. Did you always know you wanted to be a surgeon? And is this part of the tinkering you did as a kid in high school having an affinity for... Well, electronics is a little different from sticking a needle underneath somebody's retina. But anyway, is that an extension of that?

Dr. Jason Commander:

In some ways. It's more of an extension of something else, which is my mentors have advised me to keep my options open about what I can do. And that very first mentor that I talked about, Dr. Parel, I was working in his lab and he's a PhD scientist. He said, "Jason, make sure you get your MD too because I have to rely on the MDs to test what I've come up with and you should really get an MD too." So I did. I got an MD and a PhD, a combined program, and that was great advice because I love being at the intersection between the lab and the clinic.

It's just so exciting. And part of what is so exciting is the potential for helping people. I love the technical things and I can stay up all night doing a computer program or a data analysis or whatever. But I remember one time we were doing an experiment on animals and we were trying to come up with a

new way to deliver gene therapy to the inner retina, like for optic nerve disorders or glaucoma or whatever.

And I looked into this eye and I saw that the gene therapy had turned the retina fluorescent like it was supposed to, but this was the first time we'd ever seen the inner retina glowing like that green fluorescent protein. And I turned to the fellow that was next to me that was helping me and I said, "Wow. I think this is going to help people someday." And it was just a very special moment for me. This whole field is going through this transformation of gene therapy hitting the clinic and starting to work.

And because of this interest... So I'll give you a related story. When I was a resident, I had heard about the early work on what's now Luxturna. Dr. Eric Pierce, who's the director of the Ocular Genomics Institute here, used to be at Penn with Jean Bennett and Al Maguire and the whole team there that have been working on Luxturna for like 30 years now. And I was excited about that because the potential for gene therapy to actually work was amazing for these molecular diseases that we're trying to help people with.

So I got in contact through Dr. Pierce to Dr. Maguire and I said, "Can I come watch one of your surgeries?" I was in residency at the time. And there was no reason for me to go watch. I wasn't doing anything or helping anything. And he very graciously said, "Sure. Come to Penn." And so I went to Philadelphia and he brought me into the OR. And I watched him deliver what's now Luxturna to a clinical trial patient. And it was amazing. And I was like, this is what I want to do. And I was so inspired.

I came back and I decided to do my next grant was about inherited retinal disease research. And it was so important to me that I wanted to be able to take whatever we came up with in the lab and see it through to the people. And also, it's such a joy and it's maybe selfish, but it's such a joy to be able to help people like that. I love treating patients with Luxturna. It's so rewarding. I'm going on and on, but you can just tell how special all this is to me.

So when people come back after being treated with Luxturna, not everyone, but a fraction of them describe how they can see better at night now. Sometimes I feel like they almost didn't appreciate how miraculous this is. And I say, "People have been coming to this clinic with RP and LCA for like 50 years, and you're one of the first few people who have ever gotten better." And they're like, "Oh!" So being involved in all this makes all the surgery training and the time that I spent building up to that worthwhile.

Ben Shaberman:

Yeah, that's a great point. A lot of the people who are getting treated are pretty young and they don't have an appreciation for how long this journey has been to get to this point. And I think the other important point is that the success of Luxturna has really provided affirmation and a path forward for other gene therapies and genetic therapies to move forward. But I want to just get back to a point that I made earlier introducing you that you delivered the first FDA approved gene therapy, which was Luxturna.

You were the first one to deliver that. And that wasn't just for the retina, that was the first FDA approved gene therapy for any inherited condition. So that was a huge milestone. I don't know when you were observing Al Maguire and team several years ago if you had imagined you would be in that place to be the first to deliver the actual Luxturna, but that's pretty exciting.

Dr. Jason Commander:

You're exactly right. So I was assuming this whole time that since he's been working on it for 30 years, that Al Maguire would do the first one. But somehow his hospital got caught up in some red tape and

they weren't able to do it. And I asked my wife if I should rearrange my clinic schedule so that we could do it right away. And she's like, "Yes, you definitely have to do that." So I give her credit for us being the first one. But it wasn't just about us doing it first.

It was really eyeopening to be involved with the commercial rollout of a gene therapy with all the logistics and the insurance companies and all this stuff that we don't deal with during the clinical trial stage of things. So let me give you an example. The surgery was set up for Wednesday and the patient was ready. The OR was booked. I was booked. The hospital had called media because this was a milestone. And so they were coming. And then I get a call on Monday from the insurance company, one of the medical directors at the insurance company.

He said, "There's a problem with the genetic testing for your patient." And I said, "What?" I said, "Oh, you approved it already." He said, "Well, I know we approved it, but we're going over it again and your patient doesn't qualify for the treatment." And he said, "Well, it says right there on the genetic testing report that you have a variant of unknown significance in the RP65 gene." I said, "Well, that was before they formalized the vocabulary for this, and it says right next to it that it's likely pathogenic.

So it's likely pathogenic." He said, "Well, I'm sorry, I can't approve it." I was like, "Well, wait a minute. We'll get you more information." He said, "Well, call me soon because the shipping deadline is in two hours," and I'm thinking of OR schedule and the reporters coming and the patient. And so we did it. We had a genetic counseling emergency, and our genetic counselor, actually it was a genetic counseling assistant, issued a new genetic report within an hour, updating the terminology of it, and sent it back.

And then we got approved and they shipped the drug and we did it. And the reporters came. And most of all, the patient did really well. I smile every time I think about him and the whole experience. But then there was other things. Because of this exposure, I got on an insurance panel to try to get guidelines for who should get Luxturna and stuff like that. So talk about being in the right place at the right time. All 99.999% of the credit goes to the team at Penn who invented Luxturna.

Ben Shaberman:

Well, that's very humble of you to say. But the insurance story, who would've expected such drama at the last minute with the insurance company? But I guess maybe in our world, that's not totally unexpected. But I will add just for listeners out there that I know that in virtually all cases thus far, most cases, Luxturna has been covered by insurance companies. So thanks for being the first to get insurance coverage.

Dr. Jason Commander:

It's expensive, but I'll emphasize that we haven't had any patients with insurance that haven't been able to get treated. Maybe it takes a long time to get all that data through.

Ben Shaberman:

Good points. So let's talk about vitamin A because this is a really important study. There's a long history here. And let's begin by talking about the original study that the late Eliot Berson did, and this was more than four decades ago. Can you just give us an overview of what he did and what results he reported?

Dr. Jason Commander:

Sure. Dr. Berson always told me and taught me to listen to the patients. I think that's one of many very valuable lessons I learned from him. And he noticed, this was the '80s, that people were coming in taking vitamins trying to help their RP, because there was nothing. So people were taking vitamin E,

which was an antioxidant, which was very popular as a concept around that time. And people were also taking vitamin A, which is we've all heard the stories like Vitamin A is good for your eyes.

The explorers when they came across to the new world, they couldn't see. And then they ate some carrots and then they could see the stars again. This is a night blinding disease, so maybe vitamin A helps. People were taking it. So he, like a good clinician scientist, said, "We're going to test this with a clinical trial, a randomized clinical trial," which is amazing because it's the right way to get as close to the truth as we can. So there were 600 people and they were split into four groups, vitamin A, vitamin E, both, or none.

And he followed them for five or six years, which is a really long time. So it's one of the biggest, longest, most extensive clinical trials that's been done for RP, probably [inaudible 00:18:26] And the patients were followed very carefully over this time with all kinds of tests and most notably the electroretinogram.

Ben Shaberman:

And so what did Dr. Berson ultimately conclude after that long study?

Dr. Jason Commander:

The conclusion was that vitamin A slows down the progression of typical retinitis pigmentosa, and that vitamin E makes it go a little faster. So in the '80s and '90s and 2000s and 2010s, every patient with a typical form of retinitis pigmentosa who came to Mass Eye and Ear got a packet of information that had a reprint of this study, a form where to get the vitamin A, not to take the vitamin E, and three quarters of the clinic notes talking about, okay, so if you're going to take vitamin A, you need to get your liver tested yearly.

If you have osteoporosis, you should take a break. And all this discussion about vitamins, because that's all they had back then.

Ben Shaberman:

And that was a relatively high dose of vitamin A. And it was specifically, I remember, vitamin A palmitate at 15,000 international units. But I think an important point is even Dr. Berson acknowledged that the results weren't a home run. They were relatively modest, or maybe he didn't admit that too much.

Dr. Jason Commander:

If he were here, he would've interrupted you three sentences ago and said, "It's not a high dose of vitamin A. It's only 15,000 units. 75,000 units is the toxic dose. And we've had a very good safety record with people on vitamin A in the context of yearly liver function testing." And that's true, but yet the results are modest, a modest slowing of the disease. But if it's true, that really builds up over the long-term.

He made this table, which still sits in our clinic today, of how many extra years of vision you would get if you started vitamin A. And we talked about this with patients. And so you might have side vision for 25 years instead of 20 years on vitamin A, and this was very powerfully drilled into all of our patients here.

Ben Shaberman:

Right, and that's an important point. I don't mean to discount that. But one of the big challenges is that the endpoint that he used, the outcome measure, was the electroretinogram. And can you talk about

briefly what that measures and what the limitations of an ERG, what those limitations are when trying to evaluate efficacy of a therapy?

Dr. Jason Commander:

Sure. Electroretinogram, it's like an electrocardiogram of your heart where they put the stickers on and you see the electrical beating of the heart. Except when we do it on the eye, we don't use stickers. We use a contact lens, and there's other ways to do it. And you see the electrical activity of the retina after you flash it with light. And depending on the brightness of the light and the pattern and all that, you can very elegantly distinguish responses between the two types of light sensors, the rods and the cones.

Many of your listeners might know the rods are for the night, the cones are for the day. There's other differences too. And retinitis pigmentosa in particular, the rods have trouble first, followed by the cones and other inherited renal disorders that can be different. So it's a very powerful diagnostic tool for understanding what's going on with the rods and cones. Now, it's really quite remarkable how in retinitis pigmentosa, the electroretinogram in a very orderly way goes down over time.

And by orderly, when you do a graph of the patient's cone electroretinogram over time, it gives you this [inaudible 00:22:04] It gives you this very straight line. And I have to say that the system we have here is different than the regular commercial ones, and it had a lot of care put into it. So it's not necessarily fully applicable to every ERG. But in any case, it's very good at quantifying how much functioning retina there is. So the disadvantage is it's not directly measuring somebody's vision.

So the closest thing that's correlated with it is a wide visual field test, and that's really testing somebody's side vision. So you press the button when you see the light coming in. You can say, "Okay, you saw 90 degrees to your right, but you can only see 30 degrees to your left. And with the smaller light," et cetera. So it's only correlated with that, but it doesn't rely on any human input. It's a really good measurement. So if you can show that the electroretinogram is not declining as fast in someone, it's a surrogate measure that you're keeping the retina healthy.

On the other hand, it's not proving to the FDA or some regulator or to some doctors that you've directly helped somebody's vision. But me having been somewhat impartial witness to the numbers and the correlations between the different outcomes, I really do think that it reflects what's going on inside the eye. Is that what you're asking about?

Ben Shaberman:

Yeah, yeah. So I think there are two important points. On one hand, you feel like it's a worthwhile measure of disease and, well, disease progression and the potential efficacy of a therapy, but it's not an endpoint that the regulators recognize at this point. So that's an important limitation. I think another thing you said is Mass Eye and Ear has some really great ERG equipment that may not be available in other clinics. So that's a limitation also for using it widely as a clinical trial measure.

Dr. Jason Commander:

It's been one of my projects on the back burner to implement the system that we use on modern commercial ERG so that everybody can do it, but waiting for funding and bandwidth to do too. I think that would be valuable for the community someday.

Ben Shaberman:

Interesting. Well, good to know. I will pass that information along to my science colleagues at the foundation. So those initial results came many years ago for Dr. Berson's vitamin A study, and they were always kind of controversial, or maybe not kind of, they were controversial.

Dr. Jason Commander:

They were controversial. They were.

Ben Shaberman:

There were some clinicians who said, "Sure. No problem giving vitamin A to a patient as long as you're monitoring their liver enzymes." And then there was a pretty large number of clinicians who were very opposed to it. But what actually inspired Eric Pierce, you, and the Mass Eye and Ear team to reevaluate vitamin A or to reanalyze the data?

Dr. Jason Commander:

Well, getting into the criticisms first, so one specific thing was that it was pointed out that much of the effect of vitamin A and vitamin E happened in the last two years of the trial, like years five and six. And so it was thought that maybe there's something a little off about what was unusual about what was happening in those two years, and that's made it less reliable that the effects were going to hold up. And also to make matters more complicated, there was a doctor who was giving out vitamin E as a treatment for RP.

There was lots of very contentious debate between the doctor who wanted to continue giving vitamin E and Dr. Berson who said, "Well, I have the only data that shows that you shouldn't give it. And where's your data?" And it was this whole contentious field of the generation above us that we didn't really want to tread into, but here we are. So Dr. Pierce had the idea that perhaps the reason why it was only a modest effect overall is that the people with RP caused by certain genes could respond well to the vitamin A, and some people it didn't help at all.

So maybe if you average them all together, you get a smaller effect, but maybe it's helping some people a lot, maybe it's helping some people not at all. For example, vitamin A binds rhodopsin, one of the proteins in rods, that's the actual light detector. So maybe it helps the rhodopsin people, but doesn't help everybody else, or maybe there's some subset. So the plan was to do the DNA sequencing of all the patients from the clinical trial and then see which ones it helped and which ones didn't.

Now, that sounds really simple, right? So let's just sequence their DNA. But remember, this trial was started 40 years ago. Who has DNA from 40 years ago from 600 people that did a clinical trial? Well, they were so organized here that we had all the DNA. First of all, the DNA was collected. This is the first RP biobank was here. It was like, thanks to the foresight of Dr. Berson and Ted Draija, we have freezers full of DNA from RP patients linked with clinical information. It's like a goldmine of information that we're going to get into in a minute.

So we were able to recover the DNA from so many decades ago. It was still good that folks in the lab were able to extract it, which wasn't a given, Kinga Bujakowska, Ricardo San Roman, Emily Place. There's just teams and teams of people working on this. I even hesitate to mention a few names because I'm leaving more and more out. In the end, we got the genetic solutions for almost 600 people, so almost 600 families we solved genetically their RP. And that's including some of the patients from additional trials that we added later.

Because just so your listeners know, when you do genetic testing for RP, we only find a solution about two-thirds of the time. So you don't always find the solution. But anyway, so to find over almost 600

people, the solutions linked to their clinical data and linked to whether they took vitamin A or vitamin E or both or not, it was a big momentous achievement to get to that point. And my job in it was to just do the statistical analysis to show which groups vitamin A helped. I got into it about seven years ago.

It had already been going on for like 10 years. So all this beautiful work had been done on the genetics and on the clinical trial. Oh, and we recovered all the clinical trial data too, which you might not think would even exist anymore, but all the individual data. Carol Weigel, the data manager from the original trial, worked with other folks here to recreate that database in a modern way. It was a real tour de force. And so we finally got to the point where we could test which groups responded to vitamin A.

So I learned how to do the statistics from Michael Sandberg, who's now retired, and I just volunteered to do that part of the analysis. And so I did. And something strange happened, which was that there was no vitamin A effect that I could see. I checked it and rechecked it, and we re-reconciled the data. And my first conclusion was not that there's no vitamin effect is I must be doing it wrong. Not only am I doing it wrong, I'm messing up 40 years of other people's good work by doing it wrong.

So Dr. Pierce agreed to sequence more patients. We got another statistician to collaborate in the program. We fixed things up, and it turns out there was an effective vitamin A, but smaller. And we realized some of the difference was that we had additional data from years five and six that we used. And so the critics who said that the data was a little bit scattered in the years five and six, those turned out to be right. So it was a little bit less. And then we added in one additional piece of information, which is the timing of the ERG.

So it turns out, and this wasn't known at the time of the study, that the time it takes for the cones to respond to the light can give a prediction about how fast the disease is going to progress. The ones that respond quickly progressed more slowly and the ones that respond more slowly progressed more quickly. Did I say that right?

Ben Shaberman:

I think so.

Dr. Jason Commander:

Okay. This is actually quite a large effect. So people with low implicit times have very slow progression rates. People with high implicit times progressed quite rapidly on the scale of RPs. It's a slow disease no matter what, but on the scale of many years. So when we take this into account, it turns out that by a crazy coincidence, more people in the vitamin A group had fast responding cones that were destined to do a little bit better and vice versa. So when we take this into account, the effect of vitamin A overall goes away.

And so top line, we no longer recommend vitamin A for slowing the progression of disease in RP. But just to take a little aside, this was very emotional for me. It's a little bit of a crisis, not just that we were getting back into this contentious area that I told you about where everybody was arguing about it. It was that, like I said earlier, that patients have been coming here for decades being told how important it is to take their vitamin A.

And to be honest, I felt like I was stepping on the legacy of Mass Eye and Ear and Dr. Berson, who's my first teacher, about RP and what are they all going to think when we come back and tell them that it was a coincidence. And Carol Weigel, she was part of the first study. She's been doing this for years, and now she's helping overturn this thing. But what really made me feel better about it is the important thing is that we have to do what's best for the patients. And the data is the data.

That's what Dr. Pierce says. And if the data shows that Vitamin A is not helpful overall, then it is what it is. I hope that Dr. Berson will be proud of other things that he's accomplished, even if this... He was doing the best he could 30 years ago, but now we have more information and the information is that overall Vitamin A doesn't slow the progression of RP, but there's some subgroup analyses that I can talk about if you'd like me to.

Ben Shaberman:

Well, for sake of time, let's leave it there. And I wanted to also have you emphasize that you did concur with Dr. Berson about vitamin E.

Dr. Jason Commander:

Yes.

Ben Shaberman:

That it does accelerate vision loss.

Dr. Jason Commander:

That held up that Vitamin E had a small, but detrimental effect on the progression rate of vitamin E. And so there could still be many ways that it could have been a fake out or whatever, but I do not think that our patients with typical RP should take vitamin E. A practical thing is that some doctors start people on the AREDS 2 vitamins that are meant for age-related macular degeneration.

And those have vitamin E in them and I don't think that they should be on them. Even if their macula is somewhat degenerated, they don't have macular degeneration in the sense that age-related macular degeneration that those vitamins were tested on.

Ben Shaberman:

Right. And other antioxidants like lutein, zeaxanthin, stuff like that, although there isn't strong clinical evidence that it helps, you're not opposed to that, I presume.

Dr. Jason Commander:

Yeah. So the DHA Trial and the Lutein Trial that were done here are still on the books. So the DHA Trial had a little bit stronger data than the Lutein Trial, which was a little weaker. And so when we have patients come back, they can continue their DHA or their fish oil or their dark fish intake. We haven't gone back and reanalyzed that, so technically that's still on the books, and sometimes we spend some time talking about that with patients.

But really the whole field and the whole trend is moving towards the more modern therapies, which are the gene therapies and related approaches. For interest's sake, there is a resurgence in the antioxidant theory, and there's a trial going on for an antioxidant called N-acetyl cysteine, NAC, or NACA, N-A-C-A, and those are starting to roll. We'll see if they were.

Ben Shaberman:

Right. And to get back to Dr. Berson, I think it's important to say that one of his key contributions, not only the great care he provided to patients, especially at a time when so little was known about RP and other inherited retinal diseases, but he was really a big proponent of ERGs and really drove that

measurement, that resource forward as a tool for evaluating the retina. And I don't know that there was anybody who did more ERG research and captured more ERGs than Eliot at the time.

Dr. Jason Commander:

Yes, I'm very grateful for the work that he did, and Michael Sandberg was the main physiologist who was here who worked on that ERG system. It's really a super diagnostic tool. It can be very confusing what's going on in the retina if you don't have the ERG. It's not that you can't do it. But if you said to me, "Jason, here's a new patient. Tell me how bad their RP is," you get one piece of information. I would ask for their cone flicker or electroretinogram even more than the visual field or the visual acuity, because it's so well-correlated and so well-measured.

You can tell the difference between a cone-rod dystrophy and a rod-cone dystrophy RP. And so sometimes people come in with the completely wrong labels of what they have and they're like, "Yeah, I always thought I had a central vision, day vision problem, but they said I had RP." I'm like, "Yeah, the electroretinogram says your rods are working fine." I'm a believer and it's nice to work at a special disease center where we have such good access to it.

Ben Shaberman:

That's great. And so I know there are patients out there who have been taking vitamin A for a long time. They feel it's helping. Obviously they're an N of one, so it's hard to know what would've happened had they not taken it. But what do you say to patients who want to continue on that regimen?

Dr. Jason Commander:

Right, so now we're getting out of the data zone and into the opinion zone. So I just want to make it clear, different people are going to have different opinion on this.

Ben Shaberman:

Right.

Dr. Jason Commander:

I see a lot of Dr. Berson's old patients who have been so steeped in this that I worry that if I take it away from them, then when their RP gets worse, then they're going to say, "Ah, I never should have stopped that." And then I don't care if they're mad at me, but I don't want them to regret from themselves that, oh, I made the wrong decision on that.

So I tell them, "If you feel like you're doing good on it and want to continue it and don't mind doing the liver tests and the possible increased risk of osteoporosis, then you can continue it. But just know that we're not prescribing it to new patients anymore." One of my partners here, she really tells people to get off of it. So in full disclosure, this gets into the art of medicine thing.

I think that if someone is a longtime vitamin A taker and they really think it's helping them, our safety record has been good enough that I'm comfortable with the people continuing. If they have osteoporosis, then it's another reason. There were some hints in the data that it could even be detrimental to patients with the USH2A gene or the GYS gene. But you can read in the appendix of the paper, I really don't think that those results are reliable, and I don't think it's going to be making anybody worse.

So maybe if I have an USH2A patient, I'll be a little more firm to get off of it. But what I really don't want is a patient who's listening to the podcast who has an USH2A gene to not eat carrots or something

because you can have a normal diet. I don't want any extrapolation beyond these very unstable numbers that change a lot when you add just small amounts of data about a few patients. That was my experience with the trial.

Ben Shaberman:

Right. Great points. Thanks for saying that. And I guess one other point about vitamin A is that for people with Stargardt disease and cone-rod dystrophies, which are a lot different from RR, vitamin A is thought to be detrimental. So for somebody who has Stargardt disease or a cone-rod dystrophy, they definitely should not take vitamin A. That's correct, right?

Dr. Jason Commander:

Yeah. It's not hard data based on human experiments about vitamin A and Stargardt disease, but it's generally believed that since the defect in Stargardt disease is the processing of vitamin A and vitamin A metabolites build up under the retina that you shouldn't take extra vitamin A. But Stargardt patients can have a normal diet, so they can eat carrots.

I mean, it maybe become different if we get involved into the potential therapeutic that LPS is developing. Maybe some dietary things go along with that. But for a regular Stargardt patient, you can eat a salad,.you can eat a carrot. You can eat lots of carrots. If people twist my arm, I say I draw the line on drinking quartz of carrot juice. Shouldn't do that. But yeah, that's where I draw the line.

Ben Shaberman:

Okay. Well, yeah, I don't think a majority of people out there are drinking quartz of carrot juice.

Dr. Jason Commander:

Well, I just want people to not have to worry about things that probably don't matter. It's hard enough to deal with the vision loss to now say, "Oh, I can't have carrots on my salad." It's fine.

Ben Shaberman:

Right, and a healthy diet is important for your retinas and the rest of your body too.

Dr. Jason Commander:

There's more and more evidence about that, especially for age-related macular [inaudible 00:39:41]

Ben Shaberman:

Right, right. Well, Jason, this has been an awesome discussion. It was interesting and fun learning about your career and how you got into ophthalmology and retinal research and became a surgeon. And I know the topic of vitamin A is a popular one, an important one, and I just want to thank you and the team at Mass Eye and Ear, Dr. Pierce, and all the people you mentioned and the many people you didn't mention for that great work you did in reanalyzing the data.

And not to be too self-congratulatory, but the Foundation Fighting Blindness funded both the original study by Dr. Berson and the reanalysis that you so eloquently talked about. So thank you. This has been fun. I've really enjoyed learning about your history and the Vitamin A work, so thank you for taking time out of your busy day to share all that.

Dr. Jason Commander:

Thank you so much for the opportunity to share the results with the larger community and for this forum and for all the support of FFB, which has really been invaluable. And none of this would've happened without the Retinitis Pigmentosa Foundation, now FFB. So I hope your listeners continue their support of it because it's really important and leads to a lot of good things.

Ben Shaberman:

Well, thank you for saying that. And listeners, thank you as always for tuning in. It's great to have you, and we look forward to having you back for the next episode. See you then.

Voiceover:

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