Introduction to Brain Health and Microglia

we can control that. The one critical upstream issue that has to be resolved is for people to gain the knowledge and the understanding and embrace the idea that they are the architects of their health destiny and certainly their brains destiny.

Once you get your arms around that pact and and embraced the ideas that the ball's on your side of the court, And move away from this notion of live your life however you want to, whatever's comfortable, and modern medicine is going to fix your problem.

That's a strange kind of paradigm, isn't it? We know that we need to really shift the burden of opportunity, as it were, to the individual. And that's what you do.

It's that what I do, it's the outreach is all about. Empowerment and letting people become their own architects. Welcome back to this episode of Think Well, Age Well.

I'm your host, Dr. Heather Sandison. And today's guest is truly one of the legends in brain health. Dr David Perlmutter is a board-certified neurologist, a six-time New York Times bestselling author, and one the pioneering voices who has helped bring nutrition, metabolism, inflammation, lifestyle medicine into the center of brain-health conversation.

His book Grain Brain changed the way millions of people think about food and the brain. His work has been published in 32 languages, reaching readers all over the world.

He has lectured internationally, appeared across major media, and has served in leadership roles, including with the American College of Nutrition and The Journal of Alzheimer's Disease.

On a personal note, Dr. Perlmutter has had a meaningful impact on my own career. He has helped me launch successful summits, supported my book when it mattered, and has been one of the leaders whose shoulders I stand on today.

In many ways, he helped pave the way for the work that I do. His upcoming book, Brain Defenders, is available right now for pre-order and will be launching in August of 2026. Here he focuses on microglia, the brain's immune cells, and how they can either protect or repair thebrain or contribute to the neurodegeneration when they become metabolically hijacked.

Dr. Perlmutter, welcome. It's an honor to have you here. Well, thank you. What a nice introduction. I really appreciate it. Yeah, I really appreciate you.

And so many patients do as well. I can't tell you how many patient come into my office and say, well, my first introduction to what might be going on was through one of your books.

So I'm really curious, what made you decide to focus in on microglial activation, immunometabolism, and at this moment in the conversation on brain health?

I can't really say how it happened, but my goal was to try to connect dots. My goal is satisfying curiosity to allow me to be compassionate. And the curiosity really was to try to find what unifies everything we know are risk factors that relate to making a good brain go bad.

What are those pillars of neurodegeneration? What is it that's similar in terms of mechanistically between inflammation, elevated blood sugar, a head trauma, toxic exposure, PM2.5, the list goes on.

And ultimately, I learned that everything converges on the brain's immune system. That is the lens through which each of these seemingly disparate influences ultimately leads to a state of disrepair in the It is through this unique population of cells, we call them, as you said, the microglial cells that can be either friend or foe.

We call the friends the M2, supportive, nurturing, loving micro glia. And the evil twin is the m1 configuration that destroys our synapses, damages our neurons, and actually disrupts the blood brain barrier.

The empowering part, I think, about what you and I are going to talk about today is that this shift or scientifically called the polarization between that cell being on our side or working against us is determined based upon our influences.

In other words, we, through the choices that we make and the incorporation of certain lifestyle issues, either yay or nay, help determine whether that microglial cell or the population of micro glial cells is going to be supportive or pave the way for a situation in the brain that actually leads to destruction.

And the empowering part of the whole narrative is that we can control that. There's so much we can do. You know, when I think about immunology and the immune system of the body, I feel like I could take an immunologist course every year and learn more about it.

I have a humility and a reverence for how complex that system is. And I'm curious in this context, How is the immune system of the brain different from the system the rest of body?

And where's the overlap? Where is it maybe disconnected or not? Maybe it's not. I don't know. Well, there are a lot of similarities. I think functionality shows the greatest similarities of these microglial cells to peripheral cells called macrophages that really are classic members of the immune system whose job by their very name, macro, big, fudge, eat, go around and digest away things that shouldn't be there, whether those are misfolded proteins in the brain or bacterial debris or debris left over from synaptic destruction or neuronal destruction.

And that's the similarity. There are important differences, however, but I would say importantly that macrophages also exhibit both the M2 supportive and an M1 destructive, what we call phenotype as well.

But the differences are even from their very origin, the entire rest of the immune system in the body comes from the bone marrow originally. So it comes one area where the microglia cells actually arise from what is called the yolk sac.

Though they ultimately go down a similar path in terms of functionality and what influences them, et cetera, even at their origin they're coming from different areas.

They come from yolk sack, they make their way into the brain, and then they populate the brand and reproduce there. But I think that your point is very well taken, that you say, I want to take an immunology course every year just to stay up to date.

Our classic understanding of what the immune system does is, well, i've got to have a good immunity so that I can fight off the next cold or COVID, or maybe identify cancer cells and eliminate them.

All the things about the hygiene of the body, getting rid of cancer, cells getting, rid off infections that we associate with the system.

How Microglia Drive Neurodegeneration

And I think that we're moving to a place of really a broader understanding and getting away from this myopic understanding of the immune system and recognize that there's a lot of upkeep that the system does that's away reading it of dangerous elements.

And it's really a broader view, especially as it relates to what's going on in the brain, that these microglial cells,

yeah, they're doing the good things that the immune system does.

They're helping rid our brains of beta amyloid and other misfolded proteins and bacterial components and breakdown of nerves, et cetera. They're also doing really good things.

They are providing what we call trophic factors so that neurons can be nurtured and grow and replicate. Or they're providing support for the maintenance of our synapses where one neuron connects to the next synapse, and even keeping the blood-brain barrier functional and intact.

as opposed to when these microglial cells adopt what I call the evil twin phenotype, in which case they immediately digest away our valuable nerve connections, the synapses.

They destabilize the health and functionality of neurons and even work to destroy the function, important function of the blood-brain barrier. This shift from being friend to being foe is characterized by a shift in their metabolism.

In other words, how they make energy. When they're healthy, M2 supportive, their mitochondria are working really well, producing a lot of this ATP energy and keeping these microglial cells doing a great job to what we want.

But when they shift to becoming the evil twin, as it were, and damaging our brains, There are actual metabolism changes away from relying upon the mitochondria to what we call glycolysis, a different pathway by which this ATP energy currency can be produced.

That's good in the short term for a sudden release of energy, but in long run it's less efficient and it is associated with this morphology of this cell that wants to be helpful but now is being destructive.

It's spitting out pro-inflammatory chemicals, it's creating an environment within the brain that is not salubrious as it relates to brain health and functionality, and really paves the way for brain destruction.

We can actually image those M1-threatening microglial cells in living people now doing a special kind of scan called a TSPO image. And we see, for example, in Alzheimer's that the TSpO images are absolutely lit up, meaning M-1 damaging micro glial cell in comparison to a normal brain.

But what is so empowering And what has really represented for me a convergence of everything I've studied over so many years is that these images, these TSBO images showing activation of these microglial cells are seen to be positive in Parkinson's, in frontotemporal dementia, and multi-system atrophy, progressive super nuclear palsy, long COVID.

post-traumatic stress disorder, depression, major depression. So it's really across the spectrum of what makes a good brain go bad that we see this central role of the brain's immune cells activation of these microglial cells.

I know you and I share the perspective that amyloid is not necessarily the cause of Alzheimer's, right? This is part of that pathway, but not the primary causal level.

When we talk about microglia, it kind of reminds me of the conversation around inflammation, and even in the functional medicine circles, I've heard people say, Alzheimer's is caused by inflammation, neurodegeneration is cause by information, and it always makes me wonder what caused the inflammation to begin with.

And so when we start the conversation about microglia, do we run the risk of kind of going down the same path of focusing on micro glia instead of what's triggering the micro-glial into that M1 phenotype versus the M2 phenotypes?

Because even as you described, like the TSPO images, and I'm curious if those are widely available, you know, I wonder how do we use that in a really practical clinical setting to help people shift that phenotypic expression rather than just say, what we need to do is, go in there and genetically modify the expression and get every microglial cell to go M1, when really that M2 micro glia, it has Or wait, I got confused.

The M1 is the evil twin, right? And so if we're trying to get everybody to go M2, do we run the risk of not having protection, enough protection from the toxins or infections or whatever that microglia activation is trying protect us from?

I want to take a moment to share something really exciting with you. This is something that's been a long time coming for us. At Solcery, our mission has always been to make dementia rare and optional.

To give people real tools, real answers, and real hope when it comes to brain health. But one of the biggest barriers we've seen over the years is access.

So many people need this care. They're motivated, they're ready to do the work, but they simply haven't been able to afford it. And this is why I'm incredibly excited and proud to share that we are now participating in Medicare's Guide Program.

This means that for the first time, eligible patients can receive ongoing support for cognitive decline, Alzheimer's and dementia through Medicare, with significantly reduced out-of-pocket costs and support from caregivers.

We are not just opening the door, we are expanding our team to meet this need. We now have two new nurse practitioners trained in our functional root cause approach to brain health.

They're working alongside us with our teams to deliver this care in a way that's personalized, comprehensive, and deeply supportive. This is about reaching more people earlier and staying with them longer on their journey.

It's about supporting caregivers who have been carrying too much for too long. And it's about making sure that the cost is no longer a reason that someone doesn't get the care that they deserve.

If you or someone you love is experiencing memory loss or cognitive decline or has been diagnosed with Alzheimer's or dementia, I want you to know that there are options and that now there's more access than ever before.

You can learn more and see if you qualify by visiting salseri.com or calling 760-385-8683. This is just the beginning and I'm so honored and excited to be able to bring this announcement to you today.

You've unpacked a lot, and I absolutely love the curiosity here. And so it's a wonderful question. So there is a role for the M1 microglial cell. It is our first responder, as it were.

If there's an injury, if there a stroke or head trauma or infection, then we want our M cells to show up and do their job and then leave. We don't need the firemen to remain in the neighborhood once the Fire is out.

But that's the problem, that we have these other triggers that keep those microglia activated. And when they're activated, they are spewing out pro-inflammatory cytokines that further activates other supportive micro glia cells to become destructive.

So it spreads to the brain like a cancer. It needs to be shut off. I mean, you know, we've talked in how important it is to resolve inflammation with resolving mediated, pro-resolving meters.

How important is it to have an inflammatory event, but it's gotta be shut off. It's good that our brains mounted in inflammatory expression when we had COVID, for example, But when it got out of line, it needed to be turned off, Alzheimer's, as Dr.

Bredesen has said many times, is not the cytokine storm, it's the cytochine drizzle. It's just this long standing upregulation of inflammation that becomes destructive.

Again, we want some inflammation in the acute sense to help us deal with bacterial components, infections, misfolded proteins, and even cancer. But it's this long standing prolongation of this inflammatory response that gets

us into trouble.

So the question becomes, why? Why is the shift to the M1 dangerous damaging phenotype so persistent and prolonged? why is it not resolving? And that's where our leverageable inputs come into play.

Let me give you an example. In one study that looked at type two diabetics experiencing head trauma, they took a large number of individuals who experienced head drama of various degrees of severity.

And what they found was that by and large, diabolics did worse. worse outcome, longer hospitalization. Why? Because their event within their brains did not resolve quickly and the microglial cells remained activated.

Here's another example. It's called chronic traumatic encephalopathy. And it's something we see, for example, in individuals who have repeated head trauma like NFL football players.

why is it that after they quit playing football, they continue to decline? They continue to decline for exactly what you just elucidated. And that is that these microglial cells became activated with the head trauma in a very appropriate way.

Inflammation, Trauma, and Practical Biomarkers

But once the trauma had resolved, they didn't revert back to being supportive. They're still destroying the brain. There's still spewing out these pro-inflammatory cytokines and further like zombies influencing those around them.

to become the damaging phenotype as well, hence that positive TSPO image that we talked about in chronic traumatic encephalopathy. To answer the second part of your question, that TSpO imaging is not yet available for you and me.

It's purely a research tool. I can give you some very simple surrogates that will tell you whether or not your microglia are activated in terms of being destructive.

Here's one. It's called a fasting blood sugar, fasting-blood insulin, hemoglobin A1C, C-reactive protein, tape measure around your waist. All of these things are indicative of metabolic changes that present clear and present danger as it relates to shifting the microglia away from being supportive to being destructive.

So the take home message here is that we, in a very real sense, can control our brain's destiny by reigning in our micro glia, gaining control. And, you know, oftentimes In interviews, I'm asked, well, okay, Dr.

Palmer, you've talked about sleep and exercise, nutrition, getting out of nature, social connection, all the things, right? All the pillars. What's the one most important?

And I always say, the most one important thing to do, is you haven't mentioned it yet. The one critical upstream issue that has to be resolved is for people to gain the knowledge and the understanding And embrace the idea that they are the architects of their health destiny and certainly their brains destiny.

That has to happen first. Once you get your arms around that pact and embrace that idea, that the ball's on your side of the court. and move away from this notion of live your life however you want to, whatever is comfortable, and modern medicine is going to fix your problem, that's a strange kind of paradigm, isn't it?

We know that we need to really shift the burden of opportunity, as it were, to the individual. And that is what you do. That's what I do, it's the outreach is all about, empowerment and letting people become their own architects.

You mentioned the type 2 diabetes on top of head trauma and how there's different outcomes. And I think some of what you're sort of referring to there is the stacking of risk factors, but we can also stack in the other direction, right?

You can have that downward spiral or you can that upward spiral. And so let's dig into some of those practical matters. You talked about metabolism, waist circumference, hemoglobin A1C, these things we can measure.

But how do you structure? Because I know that there's so much more to it than that. How do structure an approach to systematically looking at both risk factors and ways that we could optimize so that people even know how to start, but also know to be complete?

Well, I think we'll never define complete, right? I mean, because every couple of days, there's a new variable that's important. And I really kind of shoot for the broad stroke here.

I look at the things that people are familiar with and may have already studied because I we're going to get the bulk of the work done by looking at big levers like blood sugar, and blood pressure and things in lifestyle that lead to inflammation and relates to lifestyle.

Looking at the big players, looking at sleep and exercise and diet and social connectivity and stress, those are huge. In the book, I, of course, do a deeper dive and we look at more sophisticated laboratory studies, but I think the big push is going to be the broad strokes.

The Lancet in 2024 was a fascinating report that looked at 14 variables and indicated that if we could approach these 14, in fact, all of them, that dementia risk could be reduced by about 50%. That, you know, I would take 10%. I will take, one-fifth of that.

And yet, my clinical experience is that it's probably closer to 80% of work that could be prevented. That's right. These are just the big strokes. Frankly, some of the things they talked about were not necessarily considered metabolic, but things like wearing a helmet when you're involved in an activity that puts your head at risk.

not smoking, reducing the amount of alcohol you consume, getting your blood sugar under control, blood pressure under-control, attention to hearing, and getting hearing aid.

They added this time around, because this has been done before, air pollution exposure, but interestingly, as an aside, they didn't mention nutrition.

So I, along with a couple other misrecreants, like Dr. Richard Johnson and Dr Robert Lustig, actually called them out and wrote them a letter to the Lancet and said, hey, great study on and on, must have been an oversight, but you left out nutrition and here are the citations that indicate why nutrition is critically important.

And we got a pat on the back and he said thank you for this information, we're not going to publish your letter. Anyway, but please don't distance yourself from the lancet, which was a bizarre thing.

Anyway. But that said, the point is that, you know, how deep can we go? Can we look at microtoxins? can look heavy metals, lead, cadmium, mercury, arsenic, et cetera?

Yeah, that's important. Can look other contaminants in the blood, Lyme infection, etc. There are a lot of things. The list is clearly endless. Which mouth-borne bacterium aside from porphyromonas gingivalis is important?

Who knows? So it could be a very, very long list. And that gets to the notion of knowing the patient. What might she or he really need to focus on as it relates to what's leading to their risk or already existing cognitive decline?

I mean, that's where your work really is so valuable. But, you know, I wrote a book that everyone can read and not necessarily have to go to a clinic.

Laboratory studies are now freely available, though people can ask their doctors to get this relatively simple baseline of metabolic blood tests along with things like homocysteine.

If you want to push it a little deeper, let's get a neurofilament-light GFAP and perhaps PTAW-217. But I tried to

keep it as simple as I could. But I think these are, again, broad stroke approaches, just looking at homocysteine.

I mean, if we recognize that about 28% of people have this MTHFR polymorphism and will therefore likely be at significant risk for having an elevated homocysteine.

Elevated homocistine is a significant factor for Alzheimer's and cardiovascular disease as well. And it's a simple fix. I carry the MTHFR polymorphism.

My homocysteines, when I started checking it was elevated, 11 and change. are now under wonderful control by taking methylated B vitamins and little extra methylate folate along with the folates that's in my multi and actually little methylated B12 in addition to what's into B complex.

That's what worked for me. So, you know, that gets to the notion of personalized approach to brain health. I happen to know my PTAL-217, which is lesson one, and that is good to So, you can get granular, but I think that's the book that is written.

not actually to be published. It's the book that you would write one-on-one with a patient based on how you evaluate that person, looking certainly at the big stroke, easier things to deal with.

Certainly a person is showing evidence of mycotoxin exposure, et cetera. You would agree that's a much more challenging thing to do deal, but it's nonetheless important than it is to help a personal go on a diet to keep their blood sugar under control.

Lifestyle, Risk Reduction, and Personalized Brain Health

So, you know, there's an argument to be made for, I think, both sides of this equation that on the one hand, giving the general population these really important broad strokes and at the same time, valuing, Heather, what you do in terms of the personalized approach, that is incredibly important.

Yeah, it's interesting in how we apply that at a societal level. And the Lancet Commission report obviously informs so much of what I do. I think part of it does is it helps justify our existence, right?

It's like, okay, there's this very credible institution out of the UK that's saying there are a bunch of things that we can do for dementia. It is not all beta amyloid, and that is helpful.

And yet, yeah, their list is incomplete. They have a whole section about, it was from the 2020 update, about sleep. But then they don't list sleep as one of the modifiable risk factors.

Yeah. You got to wonder. It's interesting. However, its helpful, right? It is helpful. And I think you mentioned mycotoxins and heavy metals. That's not in there, but cigarette smoke and toxic pollution exposure are.

So it'd be nice if it was sort of organized, and that helps me to systematically get through these things. We wrote to them. I think, clearly, the intent was, can we help?

Yeah. Anyway, but you know, I, think it's sort serendipitous that we're having this conversation about, you say it is more than beta amyloid, we are about 10 days out from this public cock crane analysis of the efficacy, or clearly the lack thereof, of beta amyloid targeting medications that are the go-to treatment for Alzheimer's disease FDA approved in the United States today.

The Cochrane analysis reviewed 17 studies, 20,375 individuals involved in these studies. 18-month evaluations in this studies and the benefit of these drugs was to use their quote, trivial.

They didn't find really any benefit of these drugs. Yeah, the drugs clearly worked to reduce the beta amyloid in the brain dramatically, matter of fact, but the clinical value of changing that biomarker was really nothing.

I have this in front of me and I want to read for our listeners the author's conclusions here. So I'm going to quote, successful removal of amyloid from the brain does not seem to be associated with clinically meaningful effects in people with mild cognitive impairment or mild dementia due to Alzheimer's disease.

Future research on disease modifying treatments for Alzheimer should focus on other mechanisms of action. That was the conclusion from that. We've been saying this for an awful long time.

And it's interesting that in 2020, I think it was, When these drugs were first developed, they were petitioned in front of the FDA as Alzheimer's treatments, and they failed.

There were 12 people that voted. One voted zero, abstained. 1 voted in favor of approval, 10 said no. The drugs aren't altering the course of cognitive decline.

So clever pharmaceutical people went back and said, yeah, we still got to get these jobs approved. That's all we've expended such funds to create them.

They said okay, here's what we'll do. we're going to say, petition the FDA to approve them to get rid of the beta amyloid in the brain, because as we all know, that's the cause of Alzheimer's and they got approval because the drugs do reduce beta-amyloids in their brain.

But as you well describe here in this Cochrane analysis, they don't change the downhill slide of these patients to any meaningful degree. And that is in face of of really good research.

I'm thinking of Dean Ornish and Rudolf Tanzi's report in 2024 that looked at lifestyle intervention, exercise, eating more plant-forward diet, and stress reduction in 51 individuals over the course of 20 weeks, I think it was, showing that in 70% of these people with established Alzheimer's disease, so these are the people who you give the drugs to.

Instead, they Clean up their acts, they put them on a good diet, exercise and manage stress. 70% either stabilized or improved. No person on the IV beta amyloid therapy improved, and the side effect of their treatment was some people lost a little bit of weight, their blood sugars came down, there's C-reactive proteins improved and there were some epigenetic issues I think they looked at as well that also were more favorable.

Very similarly to the outcomes that Dr. Bredesen has published that we published out of my clinic. And then also there was the Pointer trial that came out in the summer of 2025, over 2,000 patients with these lifestyle interventions improving cognitive function.

So I think it's very well established. The controversy is real here, right? And frustrating, I mean, for both of us, there's sort of this exasperation in both our voices as we talk about this.

I want to continue on the controversy line of thinking here, statins, cholesterol, and brain health. So in that 2024 Lancet Commission update on dementia, they added LDL levels.

And I think that there is this concern that, like, are we, you know, saving our brain but going to have a cardiovascular event instead, particularly when we start talking about ketones or adding fats?

And so I'm curious how you thread that needle around, how do you help people approach cholesterol management in a healthy way? I would say that it's important, and maybe that's surprising to people who've been following me for many years, but I think it is important.

I'd think that when LDL is elevated, it increases obviously the presence of oxidized LDl that becomes a significant source of inflammation in the lining of the arteries called the endothelium.

And here's the point that really matters. Inflammation anywhere in the body is not a good thing because it makes its way to the brain and can shift the microglia away from being supportive.

That's why endothelial inflammation is not a good thing. It's like a leaky gut is a not good as it relates to the brain. Now, what I've just said is it finally allows us to understand mechanistically how can gut dysbiosis and changes in the diversity and functionality of the microbiome in in a gut relate to increased risk of Parkinson's and Alzheimer's, and other brain degenerative conditions.

Why? Well, here's an explanation. Those inflammatory cytokines that make their way to the brain through the blood-brain barrier, which happens to become more permeable as we age, change those microglial cells away from being supportive to being destructive.

Activate this NLRP3 inflammasome, then we get up regulation of the production of interleukin-1-beta, this IL1B, a pro-inflammatory chemical, makes its way through the brain and further targets receptors on microglial cells to shift them away from being supportive to being destructive, whereby they now go around and destroy our synapses.

And as Dr. Bredesen has well described over many years, that Alzheimer's is a synaptopathy. In other words, the clinical manifestations are not as much from the fact that we lose our neurons, it's that, we loose our connectivity.

we lose our connections between neurons, our connection with ourselves, connections with other people, and our connexions with the world around us. So that goes from microscopic to macroscopic and it's clearly Alzheimer's is this loss of connection, which is induced by inflammation.

That can come from elevated LDL, to get back to your original postulate here. And that's why I think that we should be looking at ways of lowering LDl.

Lifestyle choices, of course, are going to be front and center. You know, some people have elevated LDL and are doing the best that they can, full on vegetarian and have genetic issues that predispose them to elevated cholesterol and LDl and may benefit from pharmaceutical interventions.

That's what I just said. Maybe not a satin on the first pass. Maybe a rapathel-like drug is reasonable or Zetia inhibit the absorption, reabsorption of cholesterol, but there are pharmaceutical issues that can be implemented to bring LDL and cholesterol down.

That's not exactly the messaging I would have given 20 years ago, but I think it's becoming clear now that this is important. Inflammation across, you know, not to mention, I don't want people to say not mention because now I'm gonna mention it.

But anyway, to mentioned that we've got to care for the endothelium and the glycocalyx within the brain as well. The glycolyx is actually the makes up part of the blood brain barrier.

and that is threatened by elevated oxidized LDL. And so I think that this is an exciting time in medicine, right? Because we don't just have statins in our tool belts.

We have supplements, we have lifestyle interventions, and then we different mechanisms of action to keep that LDL under control. And it's surprising. Sometimes people will get on a ketogenic diet.

They actually are consuming more good, high-quality fats, And we see their cholesterol levels actually improve. Their risks go down, even cardiovascularly.

And the data is also, it's confusing, right? There was a recent trial that was published that said people who are APOE4 positive actually benefit from eating meat.

Whereas in the past, we've seen others that like processed meat increases risk. How do you parse that? What you just said, I think, is very important because that's what the study showed.

It showed that red meat consumption in APOE for positive individuals was associated with a decreased risk of dementia. But making a very good point, processed meats, higher risk, of elevating your uric acid, for example, was

associate with increased risk.

You know, it's often like the discussion of, should we drink wine or not? Well, let's talk about alcohol. That's not what I said. I say wine. What about coffee?

Let's about caffeine. No, I didn't say caffeine, but coffee. Context matters a lot. When people talk about coffee, they immediately default to, well, is caffeine a good thing or a bad thing?

Not considering the other 90 bioactive components of coffee and not to mention, though I'll mention it, the polyphenol content, coffee representing the number one source of poly phenols globally in our diets.

And the absence of theanine. Pardon me? And absence the anine that is in tea. Yeah, that's true. But getting back to the recent study, looking at APOE4, I think, was that Sweden it was published in?

Nonetheless, the big default, goes to protein conversation. and it shouldn't because there's a lot going on with meat, including the fat that it contains.

Cholesterol, Diet, and Nutritional Context

We could have a discussion about TMAO in the gut and its cardiovascular issue that would be negative as it relates to you know, threatening the brain, a negative issue.

But I think the default in the conversation I've had with reference to that specific, it's funny because I was at a conference a couple of weeks back called PLMI.

We went to dinner and on the way home from dinner, I sitting in a backseat with, on my right was Dale Bredesen. He asked me that exact question. And yeah, and again, so I thing a lot of people fall back as, well, how much protein do we need?

Meat gives you a protein, but I thin context is really important. that there are other things that we're going to get from meat, like iron, or like fats, be they good or bad, depending on really how that animal was raised.

So I think it's really important not to generalize from a study saying red meat good, red meet bad. I'm grateful that they at least looked at processed meat and studied that.

They needed to. So, yeah, I think that rewrote a lot of what the messaging was for the APOE4-positive, you know, 20 to 25 percent of people in America.

The messaging that they were getting from a couple of the websites and certainly from the previous studies that had been published with reference to their dietary fat intake.

There's even some discussion these days, a publication came out quite recently, indicating that perhaps APoE 4-positive individuals should not be using an omega-3 supplement.

And that needs to be looked at. There was actually a study that came out a week ago that indicated that across the board that there may be an increased risk of dementia associated with taking fish oil as a supplement, and it was interesting.

thought about it, read the study, and thought and realized that that's not really a fair study for a number of reasons. Number one, we can't just say fish oil.

You and I know that grocery store, pharmacy store shelves have fish oils that you would never go near. I mean, just the clear bottle, the way they're marketed, you know, in the they cared for, it wouldn't go to near it.

So it's fair to look at that product as being equivalent to an Alaska cod where the liver is taken out of the cod on the

boat and the oil is harvested right then and quickly nitrogen packed or whatever is done.

That delivery of EPA-DHA is quite a bit different than, it's again like making a global statement about coffee and just focusing on caffeine. The other thing is, One other criticism that I think should be raised on thinking of writing a letter to the editor of the Journal of Prevention of Alzheimer's where this article appeared is to say, well, who is now taking fish oil supplements?

And I would think that people starting to show some cognitive issues are the ones who are gonna get a little bit more dialed in, you know, they're listening to people like you and think, I should be taking fish oil or something because that's what these smart people are telling me I shouldn't be doing.

Therefore you're selecting for a population of people who already at risk, who will already have at least subjective cognitive impairment, if not mild cognitive impairments.

So there's a lot to be criticized about that. And I think the lion's share balance of studies, going back to Martha Clare Morris, make it very clear that the risk of dementia increases in people whose blood levels of omega-3s are lower and that as an intervention, taking a good omega 3 supplement or making sure your diet is rich in omega threes, even if it's not from supplements, is reasonable and supported.

The dietary information out there is confusing at best, right? And so is there a single message? I think for me, I try to share with patients, reduce processed foods.

If it looks like it came from the tree, came form the ground, and came straight from an animal and it hasn't been heavily processed, it's not in plastic, then that's going to be better than anything that is more processed.

Right? Do you think there's that? Yeah, okay, so you agree. Is there anything else that you would add? Well, when I wrote my new book, I didn't want it to be the brain defenders diet or the Dr.

Perlmutter diet, because Lord knows there are countless diets out there, whether it's mind or paleo or mind your pale or primal or carnivore or vegetarian or med or green plus med, whatever it may be.

And it's just overwhelming for people because A, there are so many of them out there to choose from and B, once you go on that diet, it is real specific.

So my endeavor this time, was to create some very wide guardrails, but high guard rails. In other words, I recommend be on whatever diet you want that fulfills just a few criteria, and they are, keeps your blood pressure, blood sugar under control, monitor your Either wear a glucose monitor or get a check frequently or do a finger stick, whatever it may be, but get on top of that.

And whatever diet you choose that keeps your blood sugar where it needs to be. I define what that means. So a hundred is not good enough. An A1C of 5.8 is good.

Define it in the book. That's job one in my opinion. Because right off the bat, you'll take out the ultra processed foods. Cause if you're eating like most Americans do, 60% of our calories in America come from ultra-processed foods as adults.

If you are eating a lot of ultra process foods, You have dramatically bumped up your risk for Alzheimer's disease. Higher blood sugar. through this mechanism.

So that's job one. Job two is I need to see, in deference to our friend Deanna Minnich, the lots of color on your plate, i.e. fiber and polyphenols. Whatever you choose to keep your blood sugar under control, I want there to be a lot of colors on the plate.

Meaning, you know, a plant-forward diet. Eat meat if you like, have fish, chicken, whatever, eggs. A lot of plant, therefore a lot fiber. Get those polyphenols and nurture your microbiome.

P, be judicious with reference to your fat. Eat only good fats, unprocessed fats. And pretty much with those guidelines, that's the broad strokes. Can I get more granular?

Of course I can, so can you. But if people could just do that, but that is a home run. we would reduce the burden of disease. Yep. Again, I could have created the Dr.

Perlmutter diet and you're going to eat X number of times a day. You're gonna time restrict it, eat. Your gonna fast one day a week or whatever it may be.

I don't want to complicate it. I want these broad strokes to cover a lot of territory and make it easier for people. Because the biggest issue we have is acquiescence, is adherence.

to what we're recommending. And the moment it becomes too complicated, the book gets closed, and I'm done. I go back, I open a bag of chips, watch TV this afternoon, that's what I am comfortable doing.

And that doesn't serve you. So we got to keep you motivated. Right. For people who are depressed, depression is on that list of modifiable risk factors in the Lancet Commission report.

But anxiety, Depression, Dementia, they're connected through immune dysfunction of the brain. Can you help us connect those dots? Absolutely. So we discussed this earlier in the context of this TSPO imaging that lights up those activated immune cells, those microglial cells that are activated because our blood sugar is elevated, because there's inflammation in body coming from, for example, a leaky gut or elevated LDL for that matter.

I'm going to keep harping on that one because I know you mentioned that. So we see on those studies that these studies light up in major depression. What does it tell us?

Well, it sort of solidifies this emerging understanding of the role of inflammation in depression, which is really getting a lot of attention these days.

You know, Dr. Uma Naidu at Harvard has done a of work getting this information out. Dr Austin Perlmutter, my son, has made it a point. He published in Psychology Today about this.

The book Brain Energy, I think, really made clear that There's a lot going on in terms of metabolism that relates to risk for things like depression and anxiety.

And what brain energy really focused on is the mitochondrial function. And recall that we talked about at the beginning of our time together today that the function of brain cell energy producers, these mitochondria, in the brain's microglial cells, the brains immune cells is what is involved in whether they're supportive or they are destructive.

So that's what Dr. Christopher Palmer talked to us about in brain energy, how that relates to this shift and the increase in inflammation in the brain that underlies these mood disorders.

So isn't it amazing that you and I are having this discussion that he so wonderfully unpacked these psychiatric issues. And now we're talking about Alzheimer's.

I had a chat with Dr Ray Dorsey the other day about Parkinson's, But it's all the same. It's through the lens of the brain's immune system and how they are involved in metabolism.

And here's the take-home message. The metabolism of these brain immune cells, these microglial cells that determines whether they're friend or foe, their metabolism mimics your body metabolism I would say that's all I want to say, but I have a few other things I wanna say.

But we control our body's metabolism based on those levers of exercise and diet and sleep and social interaction and being in nature. Those things affect our blood sugar.

They affect levels of inflammation. Therefore, they're going to have an impact on the microglial cells. Why would being socially connected be associated with reduced risk of Alzheimer's?

Depression, SSRIs, and Brain Immune Function

Well, I don't know, maybe it's the cortisol thing, what could it be? That's kind of the question I ponder in those 90 seconds before I fall asleep at night.

Okay, so I see the literature, the Blue Zone literature that people who are socially involved, volunteering and meeting people all day long, doing things, have a lower risk for Alzheimer.

It's very significant. But why? Mechanistically what's going on? Well, what happens when you're doing things with other people? Yeah, you reducing your cortisol, that's good because that affects the microbiome and cortisol at higher levels and prolonged is damaging to the hippocampus.

We know that. Robert Sepulci's work from what, 25 years ago. But that said, Our microglial cells have on their surfaces that determines whether they're going to be supportive or destructive.

They have a receptor for something called oxytocin. Who knew? Think about it. When you feel love, when you are with other people and you're just feeling, you know, just glad to be with these people, You're playing music, your playing bocce ball, whatever it is that you doing, Your feeling joy and happiness, creating more oxytocin and that directly stimulates your M2 microglia to stay in their loving, supportive role.

So that's what's so exciting about all this science is the play out and the dot connection that we need. So many dots are being connected through this lens.

And gosh, that really is fulfilling to finally get an explanation. Not that it happens, not that there's this connection between socialization and lower risk of Alzheimer's, but now we know how it Patients are coming to us asking and confused because there is literature that suggests that taking an SSRIs and some of the antidepressants increases our risk for a neurodegenerative disease later in life.

So how do we navigate that in terms? And I think there's these really hopeful lifestyle interventions. And for someone really struggling who's maybe APOE4 positive and also struggles with depression, How do they navigate whether or not an SSRI or another psychiatric medication is a good idea for them?

And benzos, too, right? Well, I think the data on the SSRIs is not compelling as it relates to dementia risk. As a matter of fact, there's data indicating that SSRUs might actually be associated with reduced risk, and mechanistically, we know that sSRI is fairly significantly due to things.

They are anti-inflammatory, And they actually enhance BDNF production within the brain. So BdNf being this a trophic hormone being a nutrient supportive for brain cells and the growth of new brain cell and synapse formation, all of which is very good.

We call that a tropic effect of brain derived neurotrophic factor, which we can increase by involving another medicine called exercise. That's what that does, right?

So I would not necessarily put a lot of credibility into the idea that these drugs are going to be associated with a significant increased risk of In fact, again, literature suggests the opposite.

That said, I think we should back it up a little bit and ask, how effective of a treatment is an SSRI for a depression, for that matter? And we think that the literature would suggest that, the answer is, not very.

In fact, the effectiveness of SSRIs as it relates to treating depression is only minimally, if measurably at all, greater than placebo. What does it tell you?

Because placebo is somewhat effective as well. He used to say, well, maybe we should give people sugar pills. Well, I'm giving people a sugar in any form.

Maybe they could be pills to valulose or something. But that said, it tells you that there's a lot going on with respect to an individual for depression in terms of what they're thinking.

And perhaps we shouldn't be not derogating the placebo effect. Here's another way of looking at it, and you know, what are SSRI drugs designed to do? They are designed To inhibit the enzyme that breaks down serotonin Well, actually the reuptake more specifically of seratonin and ser selective serotonin ReuPtake inhibitor.

So this pathway whereby seratone it has gotten rid of is blocked, so there's more serotonin floating around. And if there is more Serotonins floating, well, by all means, we're going to be healthier.

If you believe this kind of myopic view of depression being a less seratonin happy chemical in the brain, it's between friends. It's a bit ridiculous, but nonetheless, if serotonin is playing a role, We should ask, well, then what is it that's reducing the serotonin in the brain to start off with?

And that is an interesting question because, yes, we know there are some genetic factors that are involved in that. Inflammation reduces available serotonin through the complex pathway called the kynurenic acid pathway.

But that said, inflammation diverts where tryptophan would have gone to become seratonin to a more destructive brain pathway, so that's where we should be focusing our emphasis, our understanding, and targeting where the inflammation's coming from in the first place.

We see that people who get on the ketogenic diet, their mood often improves considerably, right back to the brain energy. You bet, as they do when they take GLP-1 drugs that target mitochondrial function, get their blood sugars under control and reduce inflammation at the same time.

I'm not advocating that, though. I'm open to it. It's a tool when used appropriately. Well, no, I am open, yeah, right, for the appropriate indications.

But as I said in the new book Brain Defenders, if it gets demonstrated that this is a viable treatment for Alzheimer's, will I be recommending it? And I say yes.

Surprising. It's about keeping your mind open in the toolbox. There's no other way of generally, pharmaceutically, to unravel this problem.

Future Therapies and Personal Brain Health Habits

I mean, a multi-pronged, vis-a-vis Dale Bredesen approach and your approach has proven its efficacy. But in terms of the wider population of a single modality, Man, I mean, we saw it happen in Parkinson's, at least in a 2024 trial published in the New England Journal of Medicine using elixir cenotide, which is not an approved GLP-1 drug now in America, but Parkinson was stopped in its progression, dead in it's tracks in this one year study of 153 people with Parkinson.

Which GLPs was this? It's breathtaking. Yeah, what's GLPS, man? Pardon me? Which CLP? It was lixacinatide, and it was not available in America now, but I hope I got that right, published in the New England Journal.

I'll have to look that up because maybe there's time to get some people into. I am curious, you know, looking forward, what are you most excited about?

I know there is gamma light and olfactory enrichment and the hyperbaric oxygen and fasting and metformin and mushrooms and psychedelics. And like, I mean, the list is long and there are a lot of hope and I think there're a lots of directions that we can go.

But is there one thing that you're really excited as we look forward? Oh, I hope I don't have to do one thing, but I'm very taken by the 40 Hertz, you mentioned a gamma oscillation story, that targets microglia.

I think that has huge potential for broadspread application. It's a flashing light, for crying out loud, and can be constructed in such a way now that you don't even know it's flashing, because there's way of, in the off period, putting a different light in there such that if you really see that it is flashing.

And one of the leaders in this technology is Dr. Li-Wei Tsai at MIT. who's published a lot of the work. And she envisioned, talked about in her TED talk, the idea that these lights could be in schools and in public places and airports.

That's to target microglia. Think about that. And I'm also very taken, I guess you said what's the number one, but, you know, taken by the trend of emphasis away from ultra-processed foods.

I think that's got a lot, will have a lots of traction and a lotta play. So I, am feeling, uh, quite positive about where this can go. What brings you joy at this stage in your life?

What brings me joy? I've never been as happy as I am in life and in my marriage. We're 39 now on our 40th year. So that brings my incredible joy. I get over the top joyful that I'm going to be a grandparent.

Congratulations. Yeah, in September. unbelievable. So I find a lot of satisfaction and I guess you could say joy from the discoveries that I get the opportunity to make and publicize and hope will gain traction.

I love the opportunities I have to be in these situations to speak to smart people like yourself. You have no idea how much that lights me up. You know, that really brings a lot of meaning to my life, and that brings me joy.

I also get a lotta joy from my bird feeder, which I fill up every two to three days. And I know it sounds hokey, but I really enjoy watching the birds come to our bird feeders every day and knowing what they are.

So, little things like that. What do you do day to day, to protect your own brain health? Well, my dad died of Alzheimer's. So I know beyond my professional experience of 35 years of meeting with the families and seeing the patients, how that is, I watched him go.

And so I have that family experience that's so tragic for the 7 million families in America right now, the 55 million in the world right So, you know, I double down.

It's not do as I say, not as i do. I don't eat till one or so in the afternoon. i exercise every single day. And I eat twice a day, and I'm very careful with what I You don't want to know my supplement list because it's very compelling, but it is highlighting, obviously, things like vitamin D, DHA, K2, the B convicts that I must take for my MTHFR and elevated homocysteine, urolithin A, I'm a fan of, you know, and various other components, probiotic, et cetera.

I have a 40-hertz light on my desk that i use when I am working, Um, I try to learn new songs to play on the guitar as often as I can. And, uh, you know, dedicate to brain enrichment.

Uh, and I'm careful about protecting my brain. I stopped playing pickleball, which I don't, Which I miss a lot because I was getting injured and almost had a concussion.

So a friend of mine suggested I play pickle ball wearing a helmet. Yeah. Don't know if I could necessarily do that, but maybe I will. Who knows. And those are the things, dramatic reduction in alcohol over the past few years, that's for sure.

Not that I was drinking much before, but my reduction is down to almost none. I mean, I might have a glass of wine once or twice a week before and that almost completely eliminated, not fully, almost but completely.

And that is it. You know, i've dedicated to being a little bit more diligent about following my blood work. Um, and,

uh, you know, adjusting my lifestyle to make sure my blood sugar is under tight control.

Uh, my LDL is where it needs to be. My homocysteine is now 8.1. Um. You know my p-tal 217, I was less than 0. 1, which was good news. I maybe as a manifestation of all the things I'm doing well.

So those are the thing I do. Well, then if people were to remember one message from brain defenders, what would you want it to? You can do this. Yeah.

It's agency. Dr. Krameter, thank you so much for this conversation and also for the decades of work that you've done to move the fields of brain health forward, but particularly that last takeaway, it's really giving people back control and agency of their health, their brain health and their whole body health.

Their ability to age gracefully. You've helped us see that the brain is not isolated from the body, that Alzheimer's and other neurodegenerative diseases are not simply about plaques or tangles, but that our immune system and especially these really incredible cells called microglia may be one of these most powerful levers that we can pull to protect our brain.

So for everyone listening, Dr. Perlmutter's new book, Brain Defenders, is available now for pre-order and will be coming out August 18th, 2026. This is a practical, powerful science-forward guide so that you can protect your brain health for life.

Dr Perlemuter, it is an honor to have you here. Thank you. I appreciate the opportunity. Thank you so much for listening to the Think Well, Age Well podcast.

If you enjoyed today's conversation, please take a moment to subscribe, leave a review, and share this episode with someone you care about. It's one of the best ways to help others discover tools and inspiration for aging well.

To stay connected, get bonus resources and never miss an episode, head over to drheathersanderson.com and join my email list. Until next time, keep thinking well and aging on purpose.