Introduction to Reverse Alzheimer's and Dr. Perlmutter

Welcome everyone to the Reverse Alzheimer's Summit. It's my great honor and privilege to have my good friend and colleague, Dr. David Perlmutter. And as I was telling David earlier, he's really the person who changed neurology, as far as my feeling is, from a kind of a dead end, we don't have much we can do to wait a minute.

There are many, many things that we can address. There are many different lifestyle factors, as he says, how you're living in your 20's and 30's. And it is important, especially with the new biomarkers that come out, people are seeing earlier and earlier re Alzheimer's, preparing Alzheimer's, etc..

So it's clear that this isn't just a disease of your 60's, 70's, 80's In fact, you can see some PET scan changes in some people in your twenties and early 30.

So David, great honor to have you here. Thank you so much for being on. I could talk to David for hours and hours. We get so much to talk about, but I want to talk a little bit about your essentially your history.

You have kind of gone for it to contribute in multiple areas. And I want to start with the most recent, which is nitric oxide. So if I'm a 20 something or 30 something or a 40 something or a 50 something, none of which I am, then what am I doing about my nitric oxide to give me the best chance to keep my cognition for years to come?

Well, let me back up just a little bit, and I promise we'll get there. Why in a why nitric oxide. And I think it's really quite clear that brain degeneration is not fully related to the accumulation of a particular protein.

Yeah, that what we really do understand is that brain degeneration of the Alzheimer's type, for example, is metabolic. It's related to how the brain uses energy.

Call it a bio energetic issue. And interestingly, in the Journal of the American Medical Association back in 2020, there was an editorial that said that in the field of Alzheimer's research, bio energetics moves to the center spotlight, meaning moving away from this idea that accumulation of beta amyloid is the cause of Alzheimer's disease.

So we really need to focus on the metabolism, how the brain utilizes energy, and there are multiple pathways we could explore that topic through. But I would just mention to one is that it has to have good blood supply the brain and that it has to be able to utilize fuel predominantly glucose.

And it turns out that getting back to your question, nitric oxide is playing a pivotal role in those two areas.

Nitric Oxide, Brain Metabolism, and Oral Health

Nitric oxide allows insulin to do its job, which does other things in the brain, aside from allowing glucose in various areas of the brain to become used as a fuel, insulin is also a trophic hormone, which means it nurtures brain cells.

It nurtures the very synapses that to generate in the Alzheimer's brain. Alzheimer's being, according to my good friend Dale Bredesen, a SNAP tauopathy great word that I think you coined, but nitric oxide and I'm talking about and we're not talking about nitrous oxide that you get at the dentist talking about.

No nitric oxide is a gas so transmitter who knew along with hydrogen sulfide that there are gases within our bodies that are signaling for things to happen, that are allowing insulin to do its job, that are allowing blood vessels to dilate and allowing various organs to get a lot of blood or the blood that they need.

Now, I'll take a step back. There was a recent study that looked at the medical records of close to 7 million

individuals and did a in silico, basically an analysis comparing the drugs they may have taken with their risk of developing Alzheimer's and tried to determine are there any drugs that may be associated with a lower risk of Alzheimer's and it turns out that one drug, Sildenafil, was associated with a 69% risk reduction for the development of Alzheimer's disease.

What is this drug? Well, it is Viagra, of all things. Viagra is a drug that was originally designed to increase blood supply for erectile dysfunction, and it does so by increasing nitric oxide functionality.

And so this again gets us to understand it gets us to a place of understanding the role of this nitric oxide in terms of blood supply and in terms of allowing the brain to use fuel predominantly glucose to power its cells.

You said something I think a moment ago was really quite interesting. And it is and we've talked about this for quite some time, that the seeds are sown for brain degeneration and specifically Alzheimer's in our twenties and thirties.

That's when the metabolic consequences of our lifestyle choices begin to take root in the brain and begin to be manifested such that we can even image them by using advanced pet technology positron emission tomography, looking at glucose utilization, can predict who's already setting him or herself up for brain degeneration when they're 60, when they're 70.

So it is really so important that we recognize this important role, this fundamental role of metabolic ism or this metabolism, what I call metabolic mayhem earlier in life.

And of course, then what are those lifestyle choices that we have adopted that are either going to allow our brains to utilize fuel that metabolize well or not, and, you know, interesting, this nitric oxide story is just sort of coming on the scene right now.

We know that we make nitric oxide 50% of the nitric oxide being so important in our bodies is made in the body as a consequence of what's going on in the mouth. Wow.

Who knew that? When we eat foods that are high in nitrate or in a three, that specific bacteria that live on the top of the tongue convert that to nitrite, which is then in the body ultimately converted to what we want nitric oxide.

So in a very real sense what's going on in the mouth, the oral microbiome now, you know, we've been talking about the gut microbiome for, you know, a couple of decades now.

The oral microbiome similarly is playing an incredible role in our metabolism, not just as it relates to nitric oxide in the brain, but throughout the body as well.

And the other fact that I think is really quite interesting is that there is a chemical produced in the body that will dramatically lower nitric oxide and it is called uric acid.

And, you know, we certainly all of us in medicine have been vetting uric acid levels over the year in the context of a disease called gout, where crystals are going to accumulate in your toe joints and you're going to have a lot of pain.

You're going have to take a medication. Apparently, it's very, very painful. But we now recognize that there's a much bigger story related to uric acid, which is brought on. Yes.

By a diet that's high in certain types of chemicals called purines. But predominantly these days it's fructose, sugar, higher levels of dietary fructose, which are, you know, that's really characterizes the modern day diet, will raise uric acid and do what compromised nitric oxide and therefore compromise metabolism and pose a pretty significant threat to the brain.

Absolutely. Very good point. And so you mentioned the bacteria, the the oral microbiome. So the as you know, the dental world has coming to the same sorts of conclusions and realizing that there are a lot of things about oral health.

But now now they're all, you know, oral systemic health. This has to do with mercury levels and it has to do with oral microbiome and nitric oxide and airway and all of these things.

So we always are interested in actionable items. Do you like to see people taking or oral probiotics? Do you recommend things like dental and what sorts of things do you like to see in terms of improving the oral microbiome and improving the nitric oxide levels?

It's a it's a great question. And on the downside, as it relates to the oral microbiome would be, you know, similar to the things that related to the gut microbiome like antibiotics.

Well, you know, a lot of people are using an oral antibiotic every day in the form of a mouthwash. Yeah, mouthwash. You look at the advertisers on television or in print, our you know, what they want to leverage is the fact that this kills 99 point whatever it is, 9% of germs.

Well, let's not characterize them as germs. By and large, bacteria in the mouth are doing some really good stuff and as mentioned, are helping us have the availability of the substrate from which we are able to form.

Nitric oxide are two studies of interest that were done about three years ago, demonstrated in following individuals over a two year period of time, that three year period of time that those who used mouthwash two times a day or greater had about a 50% increased risk of developing Type 2 diabetes and close to 100% increased risk of developing hypertension.

And those are, in my opinion, strongly related to compromise of nitric oxide. I mentioned the two things it does. It's involved in the in regulating how insulin does its job, hence the diabetes and it's involved in the relaxation of blood vessels, hence the high blood pressure.

Who would think that using oral mouthwash we want to kill those terrible germs so we don't get bad breath? My gosh, of course. So, you know, and I'm certainly not saying we shouldn't be brushing our teeth, etc., I think that toothbrushing is an appropriate thing to do using a water.

I think that's a brand name and I apologize for that. But and flossing are really very important. We are seeing certainly probably a little off topic this relationship of a particular bacteria import from honest gingivalis which though tends to overgrow in the mouth the relationship of poor families to Alzheimer's, even detecting components of it in the brain, for crying out loud.

But we do see a relationship between poor dental health and higher levels of poor from gingivalis. So something to consider. We're at the primordial stages of understanding these relationships, but I think that some ideas are valuable and that is the notion of sterilizing the mouth is probably not what we should be doing.

That said on the upside, then what can we do to increase the availability of nitric oxide in the body and hence improve metabolism that is good for the brain and that is to consume foods that are rich in nitrate, that are bacteria in the mouth, can then convert to nitrate.

And ultimately we can have higher levels of nitric oxide and foods that are rich or generally colorful foods, and in particular foods like pomegranate and foods like beets, you know, you see advertised on Amazon and television, etc.

Sinus Health and Microbiome Effects

, beet based products for sports performance, etc.. And it's really based upon this very good science that ultimately you will increase nitric oxide, which will increase blood supply in this case to your muscles and throughout your body.

I mean, that was in that that science actually won the Nobel Prize in 1988. The discovery of the role of of nitric oxide in terms of allowing it was what was called first this vascular endothelial factor.

What was it that allowed blood vessels to relax? It turns out it's nitric oxide. Now we know it does. So much more. It's actually involved in regulating our blood sugar via its role in in insulin functionality.

So eating nitrate rich foods is actually a very good thing. Yeah, great point. And I remember actually many years ago at UCLA a meeting with Professor Luigi Lauro and his talking about endothelium, endothelial derived reaction factor EDI RF, which turned out to be, as you said, nitric oxide, very, very exciting stuff.

And of course, he went on to win the Nobel Prize for for that very exciting work. So let's go down to the to the sinus. It was the relationship between sinuses.

Their concern about sinus microbiome. Does it tend to be reflective of the oral microbiome? How much should people be thinking about this, utilizing it?

There have also been, of course, things like, you know, things like trying to change the sinus microbiome, your rhino's spinal microbiome, basically. What is your sense about that?

You know, it really just, I think, hearkens back to our naivete and myopia in terms of understanding that the relationships that we have with organisms that live within us or upon us, you know, in the sinuses, in the mouth, is that external or is it internal?

Is the entire digestive system really an epithelium that's exposed to the outside environment? It is. So it's really in profoundly an interface of our bodies with the external world.

And I think that some of the discussions that we have with respect to sterilizing the mouth are really relevant as relates to the sinus sinuses. I mean, people get sinus congestion and immediately are reaching for various medicinals to deal with that problem.

Vaso constrictors being, you know really I think top on the list in order to reduce the secretion of fluids into their sinuses but also steroids. And we know that throughout the body, in the skin, in the gut, in the mouth and in the sinuses, that steroids change the mental you, they change the balance of organisms and they and steroids change the the what these bacteria and other organisms are producing.

We favor the overgrowth of organisms. When we used steroids, certainly in the gut, we favor the growth of fungi we lead. It leads to increased gut permeability.

And I think we see a very direct communication with respect to the microbiome in the sinuses, in the oropharynx, throughout the oropharynx, as well as having relevance as it relates to total body health.

So we've really got, I think, morphed people away from the notion of using medications, particularly as relates to the sinuses, steroids that have really kind of devastating effects, not just with respect to the sinus related organisms, but really throughout the body.

These becomes systemic. These steroids that are injected in the nose, inhaled steroids that that are so overly, my opinion prescribed for various pulmonary issues, though there may be a time and place, that's for sure.

But I think we need to have a good discussion with patients in terms of the systemic consequences of using steroids in any delivery system. Yeah, good point.

So you mentioned earlier energetics and the critical notion that this is important for what will ultimately become Alzheimer's disease and loss of synapses.

It changes your synaptic elastic, the synaptic blasting ratio. So if you want to lower energetics, you can reduce blood flow, you can reduce oxygenation, get have someone to have sleep apnea, for example, you can reduce mitochondrial function or you can add a drag on it, which is inflammation or toxicity.

So as you mentioned earlier, PE gingivalis, you can actually see in your brain in the plaques. So these things do communicate well. Want to get to areas that are changing kind of rapidly here.

And one of them you have written a whole book about which is the gut microbiome, as you pointed out, years ago, and as Dr. Knight and others pointed out years ago, this is an area where there's a lot we don't know.

Do you want a specific species? Do you want diverse diversity is kind of the latest saying, look, you want diversity. And so if you're going to be taking if you're going to be taking oral probiotic, do you want to look at the one that survives the most?

You want to look at the one that has the most different species.

Gut Microbiome, Blood-Brain Barrier, and Alzheimer's

Do you want to focus on specific species like akkermansia or fecal bacteria and pregnancy are one of these kind of anti inflammatory ones. What is your current feeling about how to optimize gut microbiome for the brain?

Well, I think it relates back to the notion that what makes a good brain go bad would be metabolic dysfunction. And, you know, we certainly have seen a robust amount of literature being generated in the past five years relating things going on in the gut, specifically with respect to the organisms that live there and and the role of the products made of these organisms in terms of influencing our metabolism and metabolic function, even going so far as changing our gene expression as it relates to metabolism, you know, studies that have demonstrated that fecal transplant, for example, what a, you know, aggressive and bizarre sounding approach, but transplantation of fecal material from a non-diabetic individual into a diabetic, individuals showing improvements in their in blood glucose and their insulin functionality, that's pretty way out there.

But, you know, it just I think is really demonstrates this intimate relationship then between what's going on in the gut in terms of the organisms, the viruses, the bacteria, the fungi that live there in terms of their influence.

Those organisms living there need to keep us healthy because when we're gone, they're gone. And you know, everything that we do, every choice that we make in a life from a lifestyle perspective, day in and day out, whether it's stress or, as you mentioned earlier, not getting enough restorative sleep, having breathing issues, certainly taking various medications like NSAIDs and various acid blocking drugs.

Antibiotics, of course, the types of water we consume, the types of food that we consume, whether we're consuming a diet that's high in ultra processed foods or not, all of these directly impact the variety, diversity and functionality of the organisms that live within us.

And, you know, certainly one area that gets a lot of recognition is the importance of the function of these organisms in terms of maintaining the the barrier of the gut, really the gatekeeper, maintaining the gatekeepers that determine what is able to trans transcend from being a gut related chemical to getting into the body and influencing things like metabolism and certainly inflammation, a cardinal feature of neurodegenerative conditions in general.

So we take that science a little bit further and recognize that strangely these levels of metabolites coming from the gut have a role to play in the maintenance or destruction of the blood brain barrier, which regulates what can actually get in the brain and influence either the brain being healthy or not.

And to conceptualize the idea that our gut organisms are influencing the patency and functionality of the blood brain barrier, his is pretty profound.

It's it's scary on the you know from the perspective of what's going on with respect to these gut organisms these days and on the other hand, it's empowering because it allows us to conceptualize approaches to stabilize both the gut barrier and the blood brain barrier.

Something as simple, for example, as extra virgin olive oil has been demonstrated in comparison to standard olive

oil, I might add. That was I wouldn't say it was placebo, but it was an interesting study.

Demonstrate that consumption in humans of extra virgin olive oil tends to enhance the way the blood brain barrier is able to do its job. So it this is an evolving science, that's for sure.

What I just portrayed to you, I did not know at the time I wrote that the book about the gut brain connection, a book called Brain Maker. So this is a rapidly evolving area of science and it's so empowering.

It's so interesting as well. Especially one area that I find really interesting is and that is that when we talk about the incredible number of bacteria that live within the gut, but guess what?

Viruses living in the gut outnumber the bacteria 10 to 1. And viruses in the gut are, by and large doing good things. You know, everybody thinks viruses, oh, my gosh, COVID or whatever virus you want to eat, whatever virus comes to mind immediately we feel threatened.

But we have a vision, a microbiome, rather, that lives within us that is involved in guess what, regulating the activity of the gut bacteria moment to moment, such that we're now seeing interventional trials giving these various types of viruses to regulate bacterial activity and hence have a manifestation in terms of improved metabolic health.

We're certainly seeing improved memory in rodent studies whose gut bacteria are modulated with what are called bacteriophages. These are viruses that are administered to laboratory animals and and showing improvements of memory.

So, you know, there was a time we thought, well, you know, it's probably going to be a misfolded protein, end of story, when we can develop these monoclonal antibodies.

Problem solved. That didn't happen even as recently as two months ago. A third generation monoclonal antibody directed against beta amyloid was described in New England Journal of Medicine.

And while it did pretty much dramatically lower brain amyloid levels in comparison to the placebo group, the change in cognitive function was basically none.

So what's the point? And yet, when we look at the downsides, like the development of these areas or amyloid related imaging abnormalities, these areas of micro hemorrhage, these areas of swelling, etc., in a pretty dramatic in the group receiving across the board these amyloid related drugs in comparison to placebo.

And that is certainly not a free ride, especially in the context of above all, do no harm. Yeah, great point. And you know, you may have seen that the piece that just came out, a study from UCSF looking at a thousand people with PCA, posterior cortical atrophy, also called Benson Syndrome.

Professor Benson was a professor at UCLA who described this syndrome, which largely affects the parietal and occipital lobes. And it turns out to be a presentation of Alzheimer's disease, typically.

Now, the point of the article was it's not 70% that turn out to be Alzheimer's. If you look at biomarkers, it's 90%. So I use this as a way to bring up biomarkers as such a rapidly moving field and also to bring up the fact that in the paper, what they said was, well, virtually all these people have Alzheimer's disease, but there's nothing we can do about it except to give an anti amyloid antibody that might slow it up a little bit.

On the other hand, we have firsthand seen people who have who have PCA revert their PCA do well. We have a woman woman recently who got back her ability to read, who got back her ability to to work on the computer.

Someone was working with Kerry Mills Rutland, a wonderful brain health coach from New York. So again, this is part of the new era, but this ushers in the issue of when do you look at your biomarkers?

What could you give us a little synopsis of your feeling about the blood biomarkers, the p tau, the 42 to 40 ratio,

GFP Nflx, all these things that have not been available before, suddenly they are available.

My sense is that we're right at the very beginning of understanding the utility of looking at these biomarkers. And I think that as it relates to tau and amyloid related biomarkers, while interesting, I think that we need to be more upstream of that when these have started to both enter and exit shallowly accumulate.

We've already we're already in a situation where the brain is compromised and is allowing this to accumulate. These accumulate. I think it's really valuable to go upstream and there are a suite of newer related biomarker biomarkers, neural filament, light chain, for example.

One that I really like is ACL carnitine, which is involved in maintenance of membranes and fatty acid metabolism in gene expression and protein functionality, but most importantly involved in mitochondrial function.

And I think it leads me to a part of our discussion where I really want to lay my nickel down. At this stage of the game, though, maybe I reserve the right to pick my nickel up in five years when we talk again, but that is that I think ultimately we are going to see that regardless of the subtype of Alzheimer's and indeed other neurodegenerative conditions, that they are a manifestation of mitochondrial dysfunction, i.e.

an acquired mitochondrial apathy. And I think as we look at mitochondrial function are moving forward in terms of biomarkers that reflect same either measurements of free radical media dress like serum lipid peroxide, a DNA, oxidative stress, etc., protein, carbon yields, as it were, that we are going to find markers that are that are modifiable in terms of intervention that we can follow over time once we begin to target mitochondrial function.

And the reason I'm getting back to this notion of being as upstream as possible that I want to go there is because, you know, we are seeing studies in Alzheimer's using metformin which targets mitochondrial function by downregulated complex one and hence leading to increased levels of autophagy, i.e.

the the clearing of dysfunctional mitochondria which then paves the way for the growth of better mitochondria, mitochondrial biogenesis. But you know, the influence of mitochondrial function on immune function.

Naledi For example, we know that mitochondrial function that is compromised, as you mentioned earlier, by inflammation, which gets back to the gut and that's further downstream as far as I'm concerned.

Biomarkers and Mitochondrial Dysfunction

But mitochondrial function does relate to the functionality of a variety of cells in the brain that are involved in immune functionality in the brain, like the microglia that that ultimately and in peripheral macrophages as well, that mitochondrial function is a powerful determinant in terms of is that macrophage going to be friend or foe that these macrophages and in the brain the microglia exist in at least eight different isoforms but let's just say two for now a good m to characterize phenotype or functional microglial cell that wants to digest damaged proteins, that wants to assist in the development of synapses, that wants to aid in the process of growing new neurons, and then its evil twin, the M1 phenotype which fosters the growth of these abnormal proteins that tends to not support the health of neurons.

It tends to want to digest away the synapses and the difference between these two is really strongly influenced by mitochondrial function. So yeah, we learn in high school biology the power plant of the cell.

Okay, I get that. But when we now recognize that, you know, that mitochondrial function is upstream of immune regulation, it's upstream of inflammation and influenced by inflammation as well by directionally, it is highly influenced the function of mitochondria, by the things going on in, you know, in another country in the gut, things going on in the mouth and things going on related to nitric oxide, the food we eat, the care we take of our mouths, whether we're using steroids in our sinuses or not, whether we're eating a food that's high in ultra processed foods, whether we got a good night's sleep last night or not, whether we've had repeated head trauma via the sports in which we engage so many factors over which we have control right now that ultimately lead to Rome, that ultimately to are they going to be helpful or hurtful as it relates to mitochondrial function, I think are so valuable

when we can break them down and provide bullet points for individuals to understand why it is they need to exercise each day.

They need to understand what their blood sugar is doing by wearing a continuous glucose monitor. They need to take a certain suite of supplements in our our time when supplementing the foods that we eat really makes sense.

Wearing a helmet when we're involved in riding a bicycle, a scooter or snow skiing, all of these things are incredibly valuable because as I mentioned earlier, we are the architects of our brains, destiny.

And, you know, it it's where you come into play is when things have begun to manifest, when we see changes in these blood markers that are related to talent related to amyloid, and then we follow them to determine the efficacy of the intervention.

Exceedingly valuable, but I'm more inclined to think that something as simple as knowing your insulin level fasting, knowing how your blood sugar responds to your food by wearing a continuous glucose monitor and making darn sure that you're getting good sleep and measuring it wearing an aura ring or an Apple Watch, whatever it may be.

These are the actionable points that we can be taking today. John Kennedy said that the time to fix the roof is when the sun is shining. And, you know, my hope is that while individuals who are watching our time together right now, many of them are thinking about what can I do for my spouse or my mother or father or other loved one, that those who are intact cognitively can really understand that in this day in time, prevention is really the key and anyone can do it.

Great point. So I'd love to get your opinion on on some very practical matters. So number one, someone says, okay, David, you're right, you know, my mitochondria aren't functioning well.

How would you like to support mitochondrial function? I'd say that exercise would be probably the biggest thing that you can do. Okay. I think that, you know, we don't want to damage our mitochondria and we damage them when we have higher levels of inflammation in the body, when there's inflammation in the body.

A very sophisticated tool that we can use is called a tape measure. You put it around your waist and you look at the number. Well, I'm not a real keen fan of so-called BMI, but I think being overweight and certainly obese threatens mitochondrial function.

But by all means, exercise each day and get a good night's sleep and keep your blood sugar under control, I think. I'm not sure that's half the battle.

It could be 48% of the battle. It could be. Who knows what percent? But those are the big three that relate to brain health, heart health and really maintaining a healthy body in every way.

The reason it's so influential as it relates to brain health is because the brain is the most metabolically active part of the body. It's the most demanding of blood supply and insulin functionality.

You know, using variously quoted 25% of our resting energy while representing only 2 to 4% of our total body weight. But that said, it's metabolically active.

It's going to be where a metabolic issue really manifests itself. So, you know, 85, 90 million Americans are either pre-diabetic or diabetic now. And that is a situation in which their metabolism is clearly kind of want this.

And that's the medical term. But with all due respect to those individuals, pretty much becoming a pre-diabetic or diabetic is a choice. It's not something we inherited because mom or dad had it.

This is based upon how much time we spend sitting down, how much time we spend actively involved in exercise, how much sleep we get, and certainly what we eat.

And I think I emphasize sleep because I think it's really valuable to understand that sleep is hugely influential in terms of insulin functionality that very next morning.

So how do you know? I went to sleep at ten and I woke up at seven. I got a good night's sleep. Well, did you? What is the quality of sleep? How many times did you actually wake up?

How much deep sleep did you get? Which we all know is really important for the brain in terms of activity in the emphatic system. How much REM sleep did you get, which is important for the consolidation and the contextualization of our daily experiences?

We don't know that unless we metastasize our sleep, i.e. go out and buy whatever wearable device you want to buy now and find out the very next morning.

Oh, okay. I slept for seven and a half hours and here's how much time I sleep. I spend in REM sleep here, how much time I did this or that. You know, for me, I've learned some interesting things by wearing an aura ring.

I've learned that my deep sleep is really compromised. If I have a single glass of wine and, you know, we've changed our positioning on that recommendation four, which had been in place for many years.

So, you know, I'm going to say that while we enjoy the glass of wine and in an interview I did with our Dr. Austin Perlmutter, he said, you've got to think about, you know, the upsides of the social interactions that are fostered by having a glass of wine with somebody.

I get that. But for me, yeah, I recognize the polyphenols are good for me, but it immediately compromises deep sleep and I'm not in a position that I am particularly fond of that response.

Is it then worth it? Not so much. I might still have a glass of wine from time to time, but I think, you know, alcohol is a neurotoxin. We recognize that.

And, you know, at this stage of the game, nobody's getting any younger. So we I think as we age, we have to tighten up even more on the lifestyle choices that we make.

And in related questions, what do you think about Cocu? P. Q. Q. L car euro within a wall, all these mitochondrial supports. What's your take on these?

I think it's valuable to not take the coke you ten and other forms of coke you tend that are out there, you become known. You become all very you know, people are arguing one side of the other.

I don't think it's fair to take them off the table. I think we've seen some pretty darn good literature in the past that was supportive of, you know, of mitochondrial upregulation with intervention.

Perhaps the studies were not using a high enough dosage, etc.. So I think we're never going to find a single intervention to be studied and to have a dramatic effect using cocaine along with something else you measured Alka acetyl l-carnitine I think is a good consideration.

We've seen good literature as related to alcohol. We've seen really nice literature related to Urolift in a that relates to this whole notion of increasing mitochondrial function.

And in a recent report that came out about a month ago, which reviewed the whole notion of mitophagy or ridding our bodies of defective mitochondria and then allowing mitochondrial biogenesis to occur that you're olefin was listed along with a ketogenic diet caloric restriction exercise and your listen as an intervention.

So I think that looking at these in isolation may not show dramatic results. But as you have have shown us, the notion of monotherapy is really it's you know, it's it's it's past its prime.

The idea of monotherapy because it can be monetized call it like it is I think you know, allow the development of specific drugs that were home runs. But we've now got to come at brain metabolism or preservation of cognitive function and brain metabolism as it relates to an individual with a degenerative problem.

We've got to utilize multiple modalities, not just supplements and pharmaceuticals, but other lifestyle changes and throw everything we can at the at this degeneration.

And I think, as you have so elegantly demonstrated, we can turn it around. Absolutely. Yeah. You know, someone brings the car in and my car's not working well.

And you say, well, what's the one thing I can tweak to make your mate to make all the car's ills go away? That that really doesn't make a lot of sense.

You know, the this as you pointed out, you know, this is a systemic issue. It's a metabolic issue. Yes, the brain is involved. But these are all things all work together in the thought that you're just going to take one little thing and it's going to fix everything, I think is is becoming rapidly becoming outdated.

But you have to have the data, you have to assess. You have to I mean, there are some I think some universality is that we could we could throw in the mix, some of which we've already talked about, you know, the lifestyle issue.

But reminds me of the time I pulled into the gas station because I thought my my tire was low and the guy in the gas station said it looks like a flat tire, but we're going to run a bunch of tests just to be sure.

So I guess you can overdo it. But I think, you know, vis a vis your discussion earlier about what are the biometrics and you know, year by year we see new and exciting things being developed, especially related to mitochondrial function, you know, but I think some of the simpler issues that we talked about, like blood sugar and certainly insulin fasting, insulin level, etc., we want to make sure homocysteine isn't elevated.

We want to make sure B12 levels are where they need to be. There are a lot of things, but, you know, right away as we have this discussion, we are running contrary to the mainstream approach that basically people are suffering from, you know, a a drug deficiency, whether it's leukemia or whatever.

Back in the day, it was Donepezil or Aricept. You know, we almost as you need to have this or you're in trouble. No. Well, first, let's define what the deficiencies are.

We will replete those that are unique to that individual and do some genetic testing to determine what else may be going on. So where else do we need to look?

You know, look at things like MTA, IFR to determine if that person's likely to require a methylated B vitamin intervention and may have elevated homocysteine.

So there's a lot there, but I think to to really be positive. Many pieces of this puzzle are now in place. Yeah. And the the myopic view that a single drug therapy is going to be the homerun.

I would embrace that as I know you would, too. We're not anywhere near it yet. So it's going to be a multi modality approach that's already proving to be effective.

Yeah, it has to be about outcomes more than incomes so. We need to we need to look at what's working here. So what other quick thing here? Prebiotics, post biotics, probiotics.

What's your what's your recommendation for people on those? Also an excellent question. And I think that as time goes by, we're seeing advances in all three areas, you know, even a post biotic.

Practical Lifestyle Strategies for Brain Health

That's what your life in a is we mentioned era living in the context of mitochondrial function. Your lesson is the manifestation unless you buy a product.

But we're making your lesson when we eat certain foods like pomegranate, we're making your lesson from ellagic acid in the gut bacteria convert it into your listen egg, which then does the wonderful things that it does.

Good news is you can buy that as a supplement. I think we are going to see continued wonderful advancements in probiotics, primarily in combinations of prebiotics to nurture the probiotics and certainly in the arena of the post biotics or the products made by the bacteria within us as well.

You know, people are hard at it. The Exciting New Science of Akkermansia Mucin Philia. I think in terms of regulating metabolism, really very exciting.

Seeing both live products as well as pasteurized products demonstrate really significant activity. So I am exceedingly hopeful that we will recognize two things that intervention with respect to reestablishing health as it relates to our microbiomes is going to take hold more aggressively.

But also my hope is that the science that is revelatory in terms of how we are damaging our microbiomes today will take hold as well. You know, recognizing that that that drugs that are so commonly taken like NSAIDs, for example, taking an end said non-steroidal anti-inflammatory drug like ibuprofen, has a profound effect on the gut bacteria and people who are chronically taking that type of drug for their arthritis, pain or other issues have a very significant increased risk of dementia and stream of vascular disease.

Having a stroke. You know, the same thing holds with acid blocking drugs that people think they need to take because they had indigestion after they consumed some horrendous food.

You look at the television commercial, people are eating awful foods and then they pop a pill over the counter. These drugs are not a free ride and these studies are published, but yet, you know, they don't enter the mainstream and you're right, it's I forget how you said profit versus what you said something earlier that I want to try to remember, and that is.

Income versus outcomes. Income versus outcome. Yes, it's the income of people who are involved in the distribution of these drugs versus the outcome that I just described.

So about care and the care and feeding of these organisms that have, you know, your interest, your health in mind. You know, we say when a woman is pregnant, she has to be careful now as as if she didn't before, because now you're eating for two.

Well, we're each eating for billions, everything that we consume is affecting the billions and billions. I sound like Carl Sagan of organisms that live within us and upon us and are directly involved in keeping us healthy, that are directly involved in the expression of our DNA, our life code.

And we there can, you know, choose to ignore that information or embrace it as empowerment. So, you know, interesting that we come back to the microbiome.

Yeah. And as you said earlier, this idea of anti-aging, everything now about reversing your age and you know, is that really going to get rid of these problems?

You know, we'll see. It's going to be very interesting to see. You know, so far it's looking at a couple of years. You're not looking at decades. Cellular Reprograming may do that for decades, but are you really going to clean up all the thinking about that?

Yeah. What? Thinking about that? Yeah, really? We will see. We're Doctor Sinclair and the Yamanaka factors go. Yeah. Well, you know having said that, I think that depending on what metric you use, are you looking at telomere length, are you looking at methylation clocks?

Are you looking at functionality? To me, functionality is probably the most valuable thing to look at. I mean, how functional are people? How is their balance? How is their endurance?

How fast are they walking? What is grip strength, what is called copy function? You know, the term that you, I think coined, how are they working cognitively?

I think these metrics, functional metrics are very, very valuable. And should there be stabilization or improvement in these? To me it's then, you know, you're accomplishing job well done and and we will see where the methylation clocks go.

Yeah, but interestingly that you looked at shared cellular reprograming, you know, we know that's going to be in relation to human health decades away.

But wow, that is some amazing science that for sure having said that, there is something a little closer on the horizon where we we recognize that over time we accumulate.

Yes, our telomeres shorten yes, we accumulate these methylation changes on our DNA, but we also accumulate cells that are in a state of what we call senescence.

And as our cells and as our cells change, they can either die, undergo apparatuses, pre programed, cell death, they can replicate suddenly, quite aggressively.

We call that cancer that's on the other side of spectrum or they can enter a stage that should not be called dormancy, but a stage in which they're doing neither.

They're not dying and they're not proliferating. We call them senescent cells, and they're not dormant because in this situation, these senescent cells are creating products that are influencing neighbor cells.

There the cells enter a phenotype, senescence, associated secretary phenotype, sass, meaning that they're secreting chemicals that are doing bad things around them.

And, you know, we're getting a lot of new understanding that the accumulation of these senescent cells over time really is important as it relates to the aging of the human throughout the body, there are now techniques created to measure them, measure their, you know, the accumulation of these and then measure the effectiveness of so-called analytic therapy therapies that are designed to actually rid the body of these nascent cells.

One biomarker developed at the buck, I think has some promise. A lipid based biomarker, but certainly beta galactose. This is being used now in other laboratories.

So I think that as we look at the notion of of treating these senescent cells or getting rid of them or modulating them in terms of their activity by genetically manipulating them and certain chemicals can do that.

This is so that's the difference between a center lytic therapy and a center morphic therapy. But, you know, may allow us to use existing supplements like Quercetin, for example, or a pharmaceuticals like the cinnamon, which is being used.

These are in combination D and Q, not D. Q that would be Dairy Queen are are being evaluated in clinical trials now to get rid of these senescent cells in the human body and determine what the outcome may be.

So it's a lot of interesting things that are developing and we just have to do the best. You and me are you and I have to stay as healthy and cognitively intact as we can so that we can ultimately leverage these new technologies and message to the anyone listening that, you know, these things are on the horizon.

Yeah. And I think we should note while you're on that, that both the senescence Associated Beta Gal and the Sass were discovered by the late Judith Campisi, a tremendous professor who actually I recruited to the book many

years ago, who came over from Berkeley and contributed tremendously, including those two critical discoveries.

So thank you. Thank you, Judith, for that for that tremendous work. Let me finish with Chrono Biology, because there's again, more and more it's an interesting area when you eat is important, not just what you eat.

Tell me a little bit about what you recommend. Two meals a day, three meals a day, one meal a day. What times do you think are best and do you think that metabolic flexibility is important?

And do you think that ketosis is important at time?

Chronobiology, Fasting, and Metabolic Flexibility

These are all obviously related to brain health, so I'll finish up with that. The answer to I guess all the questions is yes. I think that when we look at the work of Dr.

Sachin Panda and many, many others that, you know, our DNA and therefore our physiology and metabolism is included in that has evolved as a as a consequence of the selection process that has formed the DNA that we have today.

And, you know, for 99 point who knows what percent of the time that we've been on this planet, we have interacted with our environment and have been informed by our environment in such a way as to assure our survival and our ability to reproduce in our environment.

Includes big things like the time the sun comes up and the time the sun goes down and the availability of certain foods that are seasonal, for example.

And to be fair, we've lost that connection in a very big way. And as such, we are influencing our physiology and our genetic expression in ways that it is not able to function appropriately and certainly not able to adapt.

So, you know, we pretty much have a Paleolithic genome. If not, it's certainly a Neolithic genome. And, you know, influencing that genome, the expression of that genome and our physiology based on modern day influences like light in the evening and staying up late to watch TV and eating late in the day and, you know, really eating foods that have such a negative interface with our physiology and our genome, I think threatens health. So humans traditionally, as hunter gatherers mostly gathered, though, did hunt but, you know, we traditionally were or beings that functioned in a life of feast and famine.

And as such, the notion of not being confronted, famine, but being in a state where we're not supplying ourselves with food for periods of time, primes the body to be healthy.

So that it can survive and therefore be smart enough and adept enough and strong enough to get that next meal. And aren't those three things that we really want to have going for is to remain healthy, to be smart, to be adept and to be strong.

Those are the keys to health. And therefore, I think to emulate or simulate the lifestyle of our ancestors. Getting back to the work of Dr. Lauren Cordani, who really, you know made us aware of this sort of paleo idea that we're trying to present to our genome a an environment for which it would be most conducive to health, I think has merit and and therefore going to sleep when the sun goes down.

And that, of course, changes based upon your latitude in time of year, of course, you know, but getting enough sleep, getting back to what we've talked about earlier and making sure that that sleep is restorative, is the most salubrious type of approach we can get.

And timing our meals such that we do challenge our bodies with a fast as frequently as possible. Now, when I say fast, people think, oh, you know, 40 days and 40 nights.

No, I'm talking about 12, 14, 16 hours, meaning extending that period of time between dinner and break fast. When do you break that fast? And, you know, my practice is to generally not eat before noon.

And we have an early dinner. We're now early bird, special people. And if we go to a restaurant, we're getting the early bird special. Like, I feel like I'm on a Seinfeld episode.

But yeah, most we mostly eat at home and we eat early, and then you don't go to sleep with a full belly because that does just doesn't feel right and it's not right.

You know, it's you really shouldn't be doing your major load of digestion at bedtime. Your brain's got a lot of work to do at night, and that food should be fully digested and available.

The brain needs to be fueled. When we sleep, our brain is doing a lot of work. People think, well, your whole body shuts down. Yeah. You know, a lot of other things are powering down, but not the brain.

And that gets back to our discussion of understanding the quality, not just the quantity of your sleep. So the answer to the question is, I think getting into ketosis from time to time is a good thing, a very good thing to maintain what you described as metabolic flexibility.

I think that's a hallmark of a physiology that's adaptable and that can deal with confrontations. You know, our life is full of confrontations when we travel, when good foods aren't available, and therefore we don't eat, which is what my default is, or we're forced to eat at times, whatever is at the conference, right, or whatever is available.

So to have metabolic flexibility I think is really very important. Dropping into ketosis is a good thing. I've mentioned a couple of reasons why enhancing this notion of a lysis or getting rid of these senescent cells and certainly as a way of enhancing mitophagy or purging the body of these dysfunctional mitochondria.

So getting into ketosis is really worthwhile. How would you know? While you can measure, you know, for me it'll I'll know based upon my blood sugar by wearing a CGM or continuous glucose monitor, which, you know, I think is really very valuable.

But, you know, truthfully, in a 24 hour fast, that's what's going to happen. How much autophagy or getting rid of all sorts of damage. So other components beyond mitochondria one activates with a 24 hour fast is I think unclear.

I think it varies with the individual, but there's really not a great metric for that. You know, everybody talks about, well, I fasted for X like the time because I want to turn on autophagy, I want to rid my body, my cells of defective component.

But how do you know? You don't know. But you know, I think we'll have good markers in the future for that. But for now, it's a good thing to do from time to time, orderly or maybe even extend that for a couple of days.

But I think the notion of time restricted eating, that's certainly a way of fasting for a period of time. I think that there's pretty good evidence that this is is something worthwhile for us.

Absolutely. Dr. David Perlmutter, thank you so much for your tremendous work over the years, which I think is is helping to lead to a reduction in the global burden of dementia, improved brain health, better prevention and better understanding.

So thank you very much. Fantastic stuff. And I look forward to our next discussion. Thank you. Dr. Dale Bredesen, good to see you as well. And as well, looking forward to seeing you soon.