Rethinking Alzheimer's: Dr. George Perry Challenges the Amyloid Hypothesis Transcript

(Transcripts are generated by AI and may contain errors)

Introduction to Dr. George Perry

Until recently, many Alzheimer's Association advocacy groups have said working for the cure. You know, you don't hear that among the Heart Association?

They don't work for the cure. They work for treating patients to give them a longer, better life. I think that Alzheimer disease, maybe in the long run, there'll be a cure, but I think that's very far out of sight.

And as long as we work for a cure, I think we're wasting our time. This is Doctor Talks, real talk from real doctors on the issues that matter to you most.

Welcome back to the Think Well, Age Well podcast. I'm your host, Dr. Heather Sandison, and today I'm joined by my friend and co-host, Dr. Robert Love.

Together, we're here exploring some of the most meaningful conversations at the intersection of brain health, aging, and hope. Our guest today is someone whose name carries enormous weight in our lives and in the field of Alzheimer's research generally.

Dr. George Perry is a professor of neuroscience, developmental and regenerative biology, and holds the Siems Foundation Distinguished University Chair in Neurobiology, and is the former Dean of Sciences at the University of Texas at San Antonio.

Dr. Perry has studied Alzheimer's disease since 1982, before I was born. That was the year I was born. Wow, you're making me feel especially old. You are especially wise and experienced, and he was the first to discover that oxidative stress is a key feature of this and related neurodegenerative diseases.

His studies identified oxidative damage, its source from metabolic and mitochondrial failure, and catalysts by iron and copper. I use this day-to-day in my clinical practice, and this work has led to a novel interpretation of the role of amyloid that instead of causing Alzheimer's disease, that it's a protective antioxidant response.

And the reason all the amyloid-based therapies has failed You can see why we are excited to talk to Dr. Perry and why we've invited him here today. Dr.

Perry is also the only known member of the Academies of Science of Portugal, Spain, and Mexico. He's also a prolific contributor to the Alzheimer's research in general, in addition to being the editor-in-chief and a founding editor of the Journal of Alzheimer's Disease, where Dr.

Love and I have both published our research. Dr. Perry, we are delighted to have you here. Thank you for joining us. I'm honored to be here and be able to speak to your listeners today.

So you have throughout your career challenged kind of the conventional thinking and the amyloid mafia, the amyloid hypothesis along the way. I'm curious, you know, this brings up some of the most complex and controversial topics in neurodegeneration.

You know, can you give us sort of eclipse notes of your career and how you ended up in this position of disagreeing with some of your respected colleagues?

Well, it isn't so much I disagree. It's that I listen to the data and interpret all of it collectively. But I think one of the reasons why I have a different view is my training prior to 1982. My PhD is in marine biology.

My undergraduate degree is in zoology, but it was basically marine biology, which meant I studied animals and other organisms in their environment and understand how they adapted to it.

And one of the key things about adaptation is that you generally successful organisms have changes that are important for their survival. There's a consequence of not having adaptations for survival, and it's called death or extinction, depending on whether you deal with the species.

or the individual. And one issue for humans is that we're definitely not going extinct, at least not in the short term. And we're super successful, maybe too successful in terms of impact on the environment.

And Alzheimer disease changes, whether it's tau changes or amyloid changes or common changes. All of the super sophisticated molecular genomics, proteomics work still lies with an idea that's over a century old.

Ellis Alzheimer's described a woman, in that case a rather younger woman, middle-aged, late middle-aged, in her 50s, who had a dementia illness and an autopsy, had plaques and tangles.

We haven't got over that. So, if you have your definition as that, it's really simple to say, oh, the plaques and the tangles cause the disease. And the genetics says the same thing, because the genetics of mutations and amyloid being associated with the disease as well as the pathways of production of amyloid, presenilin 1, presenilin 2, also play a role in amyloid production.

So you can come to this conclusion causation. But all that's been demonstrated by all this is no more than what Alzheimer himself demonstrated. Plaques and tangles are associated with the disease by definition.

The genomics show that the plaques and the tangles, or the plaques particularly, are strongly associated and play some role. They're not passive changes.

They're not just tombstones. That that pathway plays an important role. But they don't demonstrate what role it plays. In fact, the best demonstration of this was removal of amyloid.

by the antibody approach and the patients didn't get better. And you can come up with all sorts of hand waving that it was too late, too early, or too whatever it is, but no one got better.

Challenging the Amyloid Hypothesis

And it's not testable by other means. So we've still been fixated on one particular pathway. And I think it stems from the whole issue of how we approach disease.

Chronic diseases are quite different than acute diseases. They are not necessarily single factorial. and that they really mesh with the biology. It is not the same thing as getting hit in the head, either getting better the next day or dying, or having major brain damage.

Instead, aging is associated with multi-compensations, and all of us that are over 40 know that we change as we age. And yet we maintain normal function, some of us beyond 100 years of age.

Whether you have amyloid in your brain or not, maybe that's signaling that the brain is responding. So that's been the basis of my studies. I didn't come to that conclusion just because I was trained as a marine biologist.

I came to it by looking at the effect of amyloid on cells and on animals. in various formats and found that it actually could be neurotrophic, that it could be cause gliotic responses, and also has a strong antioxidant response in terms of how it interacts with metals.

And antimicrobial as well, right? Correct, but those are not my studies. So you've contributed, again, prolifically to the research by, it sounds like applying the principles of just good science and wanting to understand what is true, not wanting to prove a hypothesis, but really from a genuinely curious perspective of what is going to work, what is

going to support neuronal health.

And the field in general, as documented in the journalist Charles Piller's book, Doctored, really describes you. You're a leading character in this book, a hero, if you will.

It describes how the field has really gone awry, especially from a research perspective. Can you speak to any of that and where we went wrong? Well, first, you made a very good point.

One of the key lessons I learned from the time I was a graduate student, when you're trying to prove proof and quote mark something in science, the best way to do it is to try to disprove it.

you try to do everything you can to show your original ideas wrong, which I think is pretty schizophrenic because there you are, you know, tying yourself to an hypothesis and then you show it's wrong.

But you know what? You move on. You modify the hypothesis and modify it not in untestable ways because, you know, most of the exciting things of life Like, you know, whether my wife really loves me and whether my kids are wonderful or not.

How is those things testable? They're not testable by science. Uh, number one, I only have one wife, so that's an N of one. So all of these things, you know, religion is the same way.

Doesn't mean that they're not meaningful, but if you do things only to show what your your original hypothesis is true rather than to show it's not true.

You know, so the vaccine doesn't work. the approach with the antibodies. Well, what do you do? You change your hypothesis, but you don't change it to say, oh, well, we didn't test it in the right way.

I've seen it quoted saying, ah, the theory wasn't wrong. We were the ones that were deficient in our testing of it. That's not the way you do science.

The way you do science is you develop ideas that fit the data. And you mentioned the idea of amyloid being anti-microbial. Well, if it's antimicrobial, why is it causing the disease?

I picture amyloid as being much like an inflammatory response. You have an insult, and the insult that all of us hopefully experience, which is aging, Right?

If we die at, you know, 30, we don't experience very much aging, but if we live longer than 35 or 40, we're going to experience some aging and every year it's going to be worse.

No matter what we do. Yeah. If we change our nutrition and we'll talk about that later and things, we can delay and certainly have a better aging process, but still every day we're older.

And that insult, it's like getting hit in the head a little bit every day, not enough to kill you at any one time. And that's what I view all the changes of aging be.

The responses that are there, and if those responses are inappropriate, which may happen with people with mutations, because mutations that lead to disease basically are defects.

And that puts them outside of evolution. You know, many of us have mutation and outside meaning those people would be selected against. And that is the case for amyloid precursor protein, presenilin-1.

Generally, the families are very small, which says that there's selective disadvantage. I mean, the exception is this family in Colombia where it's not actively selected against and not viewed as negative.

So they have a large family. The same thing was true in Venezuela for a prion-related family, that it was very large.

But most families that have major mutations would have a problem in reproduction, and therefore they would be limited in extent.

I wanted to ask you some specific, some controversial things in the book, the book Doctored. Let's see if I can answer them. I recommend everyone read this book.

It's written like a murder mystery novel in science and basically details how billions of taxpayer dollars have been wasted on the fraudulent amyloid hypothesis because some researchers prioritize their own fame and fortune fudge their data, flat out made up their data and this misdirected funds and it got the wrong pharmaceuticals developed.

Then the pharmaceutical companies start making up their data and they start paying journals to publish their stuff. Then their stock goes up because they're in bed with the journal editors, not you.

So you were the hero in this book. Not only did they show how your journal does a very good job in peer review, Right. Some journals, if you pay, if you basically, if you pay the journal, they publish your stuff really quickly without reviewing it.

And pharmaceutical companies were basically doing that. Your journal doesn't do that. Your journal is very good peer review. And then you were helping review some of the science to help, uh, help the author Charles Piller figure out what was fraudulent.

So I'd love to hear. So I highly recommend this, this book to everybody. It's awesome. I'd love to hear what is your story with the author and, uh, Dr.

Schrag and, and what was it like being part of this, of this great murder mystery to help reveal some of the fraudulent science that's misdirected our field.

Well, you know, it's not straightforward. They mentioned particularly one particular article. And when Charles called me about this article, and this was the one about the amyloid oligomer, amyloid star, out of the University of Michigan.

It was a 2006 paper. No, University of Minnesota. So, Cold State starts with M. Yeah, well, it's close by. So, in any case, he called me about this paper and also about the work in Austin.

At Cassava. Cassava. Pharmaceutical work. Correct, correct. Kusaba's work was more limited in terms of scientific impact. It was impact was more in the business end.

But also in phase three clinical trials. Correct, correct. I view that as part of the business. Clinical trials. Human health. Correct, correct. And before you begin a phase three trial, the science should be solid.

because you're putting patients at risk, no matter even if it's validated. And this was not validated data. It really was data that was suspect. Remember, not suspect by me, but suspect by others that are expert in image analysis.

How did this happen? You know, I really don't know. I really don't know, but it's not unique. In fact, I don't think Charles Pellard deals with, there's other cases.

So I don't know how I ended out becoming asked about data issues, but I was asked about another company, I'm trying to remember their name, about suspect data.

And again, I did not render an opinion on the data. I only rendered an opinion of what it meant if it was suspect. Mainly, my comment always is that the data needs to be reproduced independently.

That is, for me, the gold standard. One is that you trust the people who produce the data. But it's been said in politics, trust and verify. Absolutely.

What really upset me was that one of the lead authors from the University of Minnesota, she was very unrepentant. She basically got rich with grants because someone in her lab.

Rich with grants and many honors, including Institute of Medicine membership. And other things. Because her co-author was cheating and she said, I didn't know about it.

Okay, be nice if you knew what you were publishing, but let's say she was innocent. But then they brought it back to her and she was, she was unrepentant.

And she said, look, you're not talking about the good things that I did. And then she tried to reproduce what she found and she basically couldn't. And they said, we can only reproduce this in our lab, but we think this is still valuable data.

And I said, boy, you really don't get it. She doesn't understand that the work out of her lab that was published misdirected billions of dollars of research, affected millions of potential patients and really affected the science.

And she's kind of bummed that she's now discredited at the end of her career rather than saying, you know what, I made a huge mistake and this was bad science.

And I'm sorry. She was just completely unrepentant about the whole thing. That's one way to describe it. Sorry, there's not a question in there, there's just outrage in there that you helped uncover.

Well, you know, along that line, though, this whole issue of the oligomer, and it's not just the 12-mer, the whole issue of amylate oligomerization, the importance in the disease, whether it's part of the disease or not is very unclear.

Very, very, it was unclear from the very beginning. One is that you'd expect oligomers to be intermediates in formation of a large fiber. It's not a surprise.

You start with the monomer, eight pieces grow. That's an oligomer. It gets longer and longer. So amyloid plaque, can you explain what the oligomer is and why that's special?

Boy, it is far more complex than this. I can tell you that for a plaque. because we've done a lot of analysis. There are tons of things beyond amyloid to apply, but let's just deal with the plaque as if it's pure amyloid.

So amyloid is a fragment of a large transmembrane protein of around 700 amino acids. That protein is cut into pieces. One piece leaves from the inside of the cell.

Oh, it goes through the membrane of the cell.

Fraud, Reproducibility, and the Doctored Book

The inside piece gets cut off and the outside piece gets cut off. And the middle, which is part of transmembrane, is the amylate sequence, which is about 40 amino acids.

That piece doesn't like to be in water. It's called hydrophobic fear of water. So it likes to stick together. Okay. And it sticks together with the other forms of itself and when it does that this is a super simplification that super little pieces come to stick together and they form a filament so you get little pieces all together if you had little magnetic balls they would stick together as magnets when they're right orientation and you have these filaments and those filaments bundled together to form a plaque okay before you get the plaque Before it gets to be large filaments, you have oligomers.

People have made the issue that the oligomers are the toxic form of the amyloid. Okay, that might be true. They're probably the more biologically active.

I don't know what it adds to the story. I never figured that out. So when he called me about this, I said this whole finding was trivial and why would anybody pay attention to it?

Then Mr. Piller pointed out that this work had been cited over 3,000 times. For those of you not in science, that's a huge number. The average number is two or one that a paper gets cited.

Over a hundred is pretty big. Over a thousand is an extremely important paper. Correct. Correct. Any paper over a thousand has major impact on the field.

And what I realized in retrospect, retrospect after I thought about it for a day or two, because I'm not so swift at thinking of new ideas, is that what I put the analogy, it was a stepping stone.

The amyloid idea that we're going to go through more as time goes on has had many folders. Many, many. And every time it folders within a month or two, or even sooner, a new story emerges.

Not a reformulation saying, oh, we should abandon it, look at it with fresh eyes. No, a new bandage. And I call them stepping stones. If you're trying, as a child, when I tried to cross the creek that went near our house, I had to go out on stones in the deeper part.

So if somebody put a stone there, it helped me get further along. And that is what the amulet theories always look for, these stepping stones, to keep it from falling into the river.

And this oligomer story didn't have to work forever. But you notice that several people are quoted, we didn't believe the theory at all. And yet they cited it after they didn't believe it.

And that's particularly disingenuous as a scientist. Of course. But then did I also understand that the oligomer theory, it's helpful, it's convenient if you're a pharmaceutical company looking for a single agent to target, right?

Yes. Is that part of the debris as well? Well, the pharmaceutical industry is looking for single targets to make people cured. Right. What they promised with the amyloid cascade is what, in my analogy, is promised to go to Lourdes, to go with a wheelchair, you get the amyloid treatment, and you get out of the wheelchair.

You know, you're treated. But to my knowledge, that does not work for any chronic condition. Whether it's heart disease, arthritis, or the others, the best we do is treatments that change the course of the disease.

Alzheimer's disease, instead of trying to look for change in the course, has actually focused on cures. And to my knowledge, there's no cure for chronic age-related disease.

Of course, we hope there will be, but we're very far from it. The best we do in Alzheimer's disease is Aricept cholinergic, which improves neurotransmitters, and the patients do get a bit better, at least some of them, and the side effects are very small.

The amyloid approach has fell short of that, and Further, one of the greatest benefit has come from Alzheimer disease is lifestyle modification. Exercise, such as the winner of the Alzheimer Prize, the Mark Smith Alzheimer Prize from Chad, we give him the prize the best publication in the prior year.

But exercise, sugar modification, lowering glucose levels, lowering stress levels, all of those things change the course of the disease, they don't eradicate it.

And if you look at, instead, until recently, many Alzheimer's Association's advocacy groups have said working for the cure. You know, you don't hear that among the Heart Association.

They don't work for the cure. They work for treating patients to give them a longer, better life. And I think that Alzheimer's disease, maybe in the long run, there'll be a cure, but I think that's very far out of sight.

And as long as we work for a cure, I think we're wasting our time. We barely understand the disease from a biological standpoint. We barely know how it relates to neuronal death, relates to synapse loss.

All the things that fundamentally have been said for Alzheimer's disease as being primary in the disease actually have very poor evidence for them. It's amazing to me that you say there's so much about this disease we don't understand.

You founded or co-founded one of the top journals in the field. on this disease. You know more about this than almost anybody. I'd love to hear why did you do that, Dr.

Perry? Why did you go about creating and serving as editor in chief of a new journal that's also been very bold in questioning the status quo? And the status quo has been extremely, you know, unsuccessful amyloid mafia style papers that haven't been very helpful.

So why did you do this? Number one, we publish papers from the amyloid as centering people. We do not exclude papers from any idea. Okay, that's really critical.

So Journal of Alzheimer's Disease was founded to form a community of investigators. For one thing, when you publish in Journal of Alzheimer's Disease, you become a member of the editorial board for a year.

And we hope that people will actually recruit articles so that it goes beyond my pedestrian interest. And the other part is we really want to embrace new countries.

You know, like third world countries, they have initiative for getting more Africans to publish. We also had prior ones for South America. And we tried to have new ideas.

That's why we, if you want to have a high impact factor, you publish things that are in the dominant idea. I'm not against having a high impact factor, but not at the expense of excluding third world countries.

and not at the expense of having new ideas. And the way we have that, we publish more articles than everyone else. This year between Journal of Alzheimer's Disease and Alzheimer's Disease Reports, which is our sister open access journal, we will publish very close to a thousand articles.

And if you look at the other journals, it might be close to this number of all of them combined, but I'm not sure. It's probably not far from it. You do publish a lot, but I want people to know that your vetting process is very strict.

It took me years to write my paper. When I submitted it, I got back some very serious feedback that took me another couple of months to incorporate. It took me at least a month to incorporate and rewrite the paper to get it accepted.

So the peer review process happening at the Journal of Alzheimer's Disease is really top notch. We try. We try. But I cannot guarantee it's always perfect.

And both regards. Nothing is perfect, right? That's not the standard. The standard isn't perfection. It's a reproducibility. And I think that's another thing that comes up in the scientific community is it's hard to get published if you're reproducing something, right?

If it's already been published. What people are looking for is often the first time it's published, that it's unique, that it's different. And if we really want to be good scientists, as you said, reproducibility is highly valued.

And that's really how I ended up in the Journal of Alzheimer's Disease with our paper, is I was looking to reproduce what Dr. Dale Bredesen had published.

I had independently conducted a very similar trial in my office, and we were showing very similar results without his involvement. So it was done independently, and it would have been hard to get published in another journal

because it wasn't unique.

But that's not the value in it. Not only that, Dr. Bredesen has had a lot of issues that people have been very critical of him. And, you know, recently there was an article in New York Times, very critical of him.

Can we talk about this article? I love this article, it's so bad. I love your take on the New York Times article. Well, you know, I'm not agreeing that everything Dr.

Bredesen says is correct. Reproducibility is also the issue. But you can't dismiss things without analyzing them. And here he's making claims that are revolutionary.

People can be reversed. Whether that means that Alzheimer's disease can be reversed, I think it still requires validation. But because one of the issues I think with Alzheimer's disease, especially in the initial phase, many cases are misdiagnosed.

People that are older have a lot of reasons to have cognitive issues. Think about it. They may have lost a spouse. They may have financial problems. They may have physical issues because most older people have comorbidities.

And if you can address many of those, you may be able to reverse the course of the disease. Instead of just coming into your general practice person and leaving with a prescription for Aricep because she didn't draw the clock right, I think really it's important to understand why people are demented.

And many of those conditions can be dealt with. And the main criticism I've had when reporters have asked me about his work, and I've been misquoted along that line, they say it's expensive.

Okay. Well, Okay, what are the alternatives? If a person becomes cemented, they're going to be in a nursing home. That's going to be incredibly expensive, either for the person involved or society.

If they get involved in these antibody trials, they're incredibly expensive and put people at risk. Dr. Bredesen's work does not put people at risk. They can discontinue it.

And the cost, from what I know of it, is not horrendous. So I just look at it in the broad spectrum. It needs to be analyzed. And further, if it is successful, it can be upscaled and probably costs can be reduced.

When you start something and it's small scale, it requires specialized training. That's one thing, but this can be reduced. Number two, this idea that Dr.

Amyloid Oligomers and Failed Drug Trials

Bredesen proposed has been around with a foundation I'm associated with, the Alzheimer's Research and Prevention Foundation, which has a more narrow treatment with four things that they suggest.

What are those four things? Four things, exercise. nutrition, stress reduction, meaning in life. So are those, you know, with the 36 things that Dr. Bredesen proposes?

Well, it's more encompassing. I'm not certain everybody can accomplish all 36, but the four things also can make a difference for people. And it puts Alzheimer's disease in the sphere of other age-related chronic conditions.

And that, unfortunately, is not the way it's been dealt with, because Alzheimer's disease is a part of our normal biology. You know, that doesn't mean becoming demented is part of our normal biology.

But what's happening in the brain is part, you know, all of us that are over 40 have some degree of amyloid already in our brain. The amyloid that we associate with Alzheimer's disease is part of our normal aging, normal biology.

Correct. Alzheimer's disease itself, hopefully, is not part of our normal biology. No, I think that that is part of the

failure. Just as heart disease is part of the failure and arthritis is part of the failure, how the body deals with changes of the aging process.

You can age and maintain normal function, which is what evolution is probably pushing for. but you can also fail along the way. And that's what I view the people with mutations, that they fail much earlier, they fail in their 30s and 40s, and people without those mutations fail in the 70s, 80s, and beyond.

Now, what was your specific thought on the Times article? So, both Dr. Sanderson and I were interviewed for that article. At length. And I thought the researcher, I thought she asked good questions.

I agree the criticism of it's expensive. Try Alzheimer's. That's really expensive. Whoever you're going to do it. That is exactly what I say. Alzheimer's disease is expensive to everybody.

Fish oil is not, so I'd love to hear your, and then they really misquoted the science. They said it doesn't work for everybody. That's true, but it really works for seven out of 10 people, according to Dr.

Sanderson's research. So I'd love to hear your thoughts on this, on analyzing the science of that article, because my concern is that that article is going to deter a bunch of.

neurologists from recommending diet and exercise to their patients saying, Hey, this is expensive and it doesn't work. Just, just take the drugs right now and eat the French fries.

Yeah. And the article ends with eat your French fries, which is fascinating to me that that's how they concluded the article. Were you interviewed by Lindsay Gelman by the journalist?

No, no, I learned about, I'd been interviewed prior. I don't remember when years ago. And that's when I said I was slightly misquoted, like I said it was expensive or something like that, which isn't what I said.

I said, Alzheimer's disease is expensive and this is, anyway, I don't think that's a big issue. Even if this only benefited 10% of patients, even if it only benefited 10% of patients, that would be revolutionary.

Even if it benefited 1% of patients. You're seven out of 10, right? Well, 74% of the participants of the – it was a small study. It was a feasibility trial.

Twenty-three participants over six months who had measurable cognitive impairment on – of course, we screened them with MOCAs, but then we also looked at the Cambridge Brain Sciences battery of neurocognitive testing.

And 74% of those participants, so 17 out of the 23, improved their cognition measurably and statistically significant improvement. across the means of all participants in six months in overall composite cognition, memory, and in sleep and quality of life.

So these have profound implications for people. I think that's why it was so heartbreaking for me to read the article after being interviewed at length.

So I asked one of my colleagues about this. who has worked in the pharmaceutical industry previously. And she told me, she said, he realized that that was a hit piece.

That the pharmaceutical industry does not want to have competition. Here they're launching these monoclonal antibodies. It is totally unclear whether patients really benefit from those trials.

And it's very clear that there's extremely high risk. Correct. All the patients have brain shrinkage. Oh my gosh. That has been true for every one of the trials.

There's 20 some trials that have been done and when people have done imaging the brain shrink. And do they call this pseudo atrophy? Do I understand? I don't know what they call it.

Is this targeting the amyloid as well? All of the studies I'm talking about are antibody studies, either they're passive immunization using monoclonal antibodies, or prior studies which used antigen.

You know, and then have endogenous animals. You do not have amyloid plaque blockers? They theoretically remove the plaque. Okay. So there's controversy on that, but let's not go down there.

So these are targeting amyloid plaque through monoclonal antibodies? Correct, correct. And it's been demonstrated There's controversy on that point, but the autopsy of one of the people who died was a close colleague of mine, Rudy Castellani.

You know, this woman that was reported in New England Journal of Medicine was sailing with the family the week before she died. and had dinner the night she was admitted to the hospital.

She went out for dinner. She was not bedridden, you know. She had mild cognitive impairment. She was a lawyer, 65 years of age. And why was she so motivated to be involved in trials?

Because she was an APOE-44 homozygote. So she was at high risk, not 100% risk. theoretically 10 times normal risk. Yeah, that is probably not a good candidate for getting leukemia.

Correct. Now we know that because you're more likely to have congophilic angiopathy. And I wrote a, together with Craig Atwood and Mark Smith, many years ago, I wrote a short letter for Science Magazine, so a prominent place, saying that the most likely outcome of treating amyloid would be cerebral hemorrhage.

Why? Because the muscle layer we demonstrated in prior studies is lost during Alzheimer's disease because it gets replaced with amyloid deposits in the vessels.

You're reducing the integrity of the blood vessel. Correct. Correct, that the vessels are already compromised by replacement of the muscle layer with amyloid.

And in fact, in some people with Alzheimer's disease that have sufficient congaphylic angiopathy, they will have stroke spontaneously. So even without removal, it's even going to accentuate the problem.

So we wrote this small note in Science and followed it with a larger article in another journal going through why this would be a likely outcome among many studies that we had analyzed that amyloid removal would be detrimental.

You called these side effects well in advance of what was likely to happen. I think that was in 2003. So we became questioning the amyloid idea beginning in the late 1990s and wrote our first article in the year 2000 and it was in the journal Lancet and it was called Amyloid Junkies being why do you think the amyloid removal will be a benefit and that the real test of the amyloid hypothesis will be when we do these trials to remove it.

And then with the failure of those trials, at that point we didn't say that the idea was wrong. They said, why are you so sure? And then we wrote, same year Copernicus revisited.

The idea, you know, Copernicus was the one who suggested that the planets went around the sun rather than the reverse. And I pointed out, which actually my co-authors, who played the major piece in writing this article, I said, do you realize Copernicus' work was published posthumously?

that if you question things like this, he was afraid of being burned at the stake, right? Because people would question, Galileo getting involved is more complicated than just him questioning it.

He was kind of making fun of the pope. So anyway, all these stories are complex, but he at least wasn't burned at the stake in his recanting. So any case later on when the antibody approaches didn't work and the initial reports said that the patients actually got worse.

The initial report said that then there was no more comments about patients getting worse. They just kept doing

more and more trials with earlier type patients and with different targeting oligomers.

Remember, that's why the oligomer story was important. The reason us, the studies removed amyloid, but they didn't remove the toxic one. I thought it actually reminded me of the whole approach of needles, angels on the head of a pen or any of those type of things.

You're looking for something that doesn't exist. and you're making up new stories. You didn't get the right one. And amylase is clearly the evil. So you need to remove the evil.

And medicine, as opposed to biology, always seems to point out something is evil. If you hear a talk that's about medicine, they talk This is the bad thing.

Biology doesn't have bad things. It just has things. And they're all related to surviving. You know, a lion is wonderful to see at the zoo. But if I was in Africa and I wasn't in a, you know, in a truck and a lion came to me, it wouldn't be a very good thing, right?

Because it's a value judgment. So it depends, for me, amyloid depends on context. I think it's doing its job, which we think plays an important role in cleaning up metals so they don't cause oxidative damage.

But does that mean it could be out of control? Of course. Of course it can be. But that isn't the rationale people show. They always point it to being evil.

And so therefore I wrote a small thing and I likened the idea of amyloid removal to exorcism and leeches. And you know, the idea of bloodletting is not so old in science.

George Washington died of bloodletting. He had a minor illness and the physician came and withdrew blood because the idea of humors, you know, this is back from Roman times.

And 200 plus years ago, that was the year 1800. So 220 years ago, probably the best of medicine. I would imagine George Washington had the best possible at that point.

Somebody came and removed his blood. And that definitely, if you're a little bit sick and you have more blood taken out, it doesn't have a good outcome and it didn't have a good outcome for him.

Lifestyle, Prevention, and the Limits of Cure

So I think that people are always trying to remove something evil. And sometimes that works. So Dr. Gray, I want to provide a little bit of context to catch everybody up who hasn't read the book, is not really familiar with the data.

So around 2000, you published an article saying, removing the amyloid plaque based upon the data is likely to increase problems in the brain, specifically strokes and problems there, because it's kind of weakened blood vessels.

And you wrote an article in The Lancet, which won the top journals in science about calling people amyloid junkies saying, listen, you think amyloids, you think this is the biggest problem with Alzheimer's, where's your data?

Let's see. And then the initial reports were, you're right. The Alzheimer, the drugs that block amyloid plaque were causing more problems than they were solving.

So that was the big first chunk of science on this. And then they kept changing the story. They said, well, maybe it's not just amyloid plaque. It's a specific type of oligomer.

And hey, we, hey, we found it in the University of Minnesota lab and no one can replicate it. But look, look how clear it is on our fraudulent science, which is what the book doctors about, it's about that fake study.

And then other people are saying, oh, and then other people are citing this study and it gets 3000 citations and it affects the literature. They said, oh, it's not just the amyloid plaques, it's the specific oligomer.

And then you got pharmaceutical companies saying, Hey, we're going to target this oligomer. And then they got their drugs and phase three trials. That's basically you.

correctly shared what was going to happen 25 years ago with your two papers, you saw this coming in advance. So thank you for warning the scientific community and the people about this.

It really didn't stop people from continuing to fund this approach. Right. If you could wave a magic wand at this stage in your career, what would you hope the next few years of research look like?

There's a lot of changes happening. I think it's yet to be determined whether they're good or bad or indifferent. There's a huge shift in how money is being spent at the NIH.

And I'm wondering if you had control over that, what would it look like? What would be emphasized? What would be studied? How would we go forward if our goal were to reduce the suffering associated with Alzheimer's and dementia?

For one, I wouldn't discontinue studies on amyloid, the basic biology, because I think amyloid and tau play a critical role in the disease. But I don't think the data does not put them as causative.

It puts them as critical in the pathway. Because usually you have people that say they either cause and they're everything or they're nothing. There's a lot of differences.

and subtleties in things. They're clearly correlated. They're clearly part of… Correlated and probably play a critical role in the pathway. Yeah. Okay.

And they may be able to provide insights. May. Okay. But there's also tremendous, like the work you've done, Dale Bredesen and others, Dean Ornish, you told me there is a long list of people.

A long list of people that put Alzheimer's disease, much like other age-related chronic conditions, in which many factors play an important role. And what we're looking at is one pathway of aging in which the system fails.

By fails, I mean fails to lead a functional brain. The brain stops functioning. except, you know, to maintain heartbeat and things like that, but it doesn't maintain normal cognition.

So I think we need to understand that much better. That means to understand the idea of the infectious agent idea, how does that play a role, the role of diet, the role of diabetes, and a much broader biological sense.

And along that line, doing more clinical trials for amyloid I don't think it's particularly valuable. Okay, I've been asked that and people are more in the government area and I wouldn't say that there, but I don't think that they provide a lot of information of amyloid removal by itself is going to make a difference.

That doesn't mean it couldn't work, but so far it wouldn't. Well, the logic used for tau is the same logic used for amyloid, so I think it's highly likely, but not demonstrated, that you'll end up with the same outcome.

Tau also is associated with an antioxidant response. It's different than the one of amyloid. It's associated with an enzyme hemoxygenase, which is an antioxidant enzyme.

Wherever you find tau in Alzheimer's disease, you find this enzyme co-localized. Why is hemes important? Mitochondria contain a lot of heme-containing enzymes, and mitochondria are getting turned over in cells, and that turnover needs to be, you have to break apart the components, and heme is one of those components.

The other component is metals. The heme is just like hemoglobin, contains iron, which is responsible for the red

color of blood in cells. There's little cytochromes, which are very similar to hemoglobin, well, in the broadest sense, and they get turned over.

because cells are constantly exchanging out the proteins that are there, renewing them. And when you renew them, you release these metals. We think amyloid plays a critical role in those inner changes.

In other words, binding the metals so that they don't cause oxidative damage. Fascinating. So more research potentially down that vein. I have a question about that.

I recently got to have a meeting with a CEO of research of a major pharmaceutical company. And I said, what are you doing with Alzheimer's? And he said, oh, we got this really great new treatment.

By the way, he's in pharma. He loved the New York Times article. He thought it was great science. And I had a few words for him about that because it was anti-science.

So I said, what does it do? He said, well, we see tau tangles as being contagious. And so if there's cells next to each other, if one cell has tangles in it, so for those of you at home, tau tangles happen inside of the cell, inside the axon.

Whereas plaque happens outside the cell. So this is problems inside the cell. So if one cell has, as tau tangles, the next cell is likely to get that.

And part of that is phosphorylation. So they have a drug, they're developing drugs that prevent the transfer of phosphorylation from one cell to another.

So it's blocking a pathway of phosphorylation. And, and they believe this will help reduce tau and this will help prevent with Alzheimer's. And my thought was, well, what's causing the tau?

You're stopping the spread of it, but what's causing it? And that this is an unwelcomed question to someone in pharma because they want, as you said, a single target and a single pill that cures everything.

So I'd love to hear your prediction because this will probably be. In the next 20 years, assuming their research shows any sort of promise, in 20 years, we'll be having this conversation about p-tau drugs.

What are your thoughts on the likely outcome of reducing the phosphorylation from one cell to another involved in making of these tau tangles? Well, number one, I don't think we're going to have to wait 20 years.

There's already studies on tau locking, and the initial ones have not shown benefit. Might it be different for the phosphorylation? Number one, you can never be certain.

Any of my conjectures with regard to drugs that might work, who knows? They might work. But if I'm making my best guess, my hypothesis is that this is still part of a normal response.

And therefore, in fact, tons of data is shown how phosphorylation occurs during early life when you're a child. Yeah, you see this, when we measure p-taus, they're high in children, and they're also high when there's neuroplastic activity going on.

Yes. So how does that sound like that's bad? So this summer marks 50 years that I've studied oxidative stress. Thank you for your contribution to science.

That's a tremendous contribution. Oh, thank you. So I began studying it in sea urchin fertilization. So fertilization is something pretty essential to life.

If you weren't fertilized, the egg of your mother and the sperm, they didn't join, you wouldn't be here today. So your genes wouldn't go forward. What happens right after fertilization is there's an oxidative burst.

And some of that is lipid peroxidation, another part of is naphthaquinone oxidation. And that's what I discovered while I was a student. And so, you know, at that point in time, most people thought of oxidative stress as being something that was bad.

And that's what I consider to be the classic idea of oxidative stress. Classic idea I call the rusty nail idea. When you're born, when you're vital, you're shiny and bright, and you're able to fight off rusting.

As you get older, you start to get little bits of rust on you. In fact, I remember asking a very prominent person about my work early on about assays because I didn't know when I was a student how to assay oxidative stress very well.

And I remember calling Al Tappel, who was an expert in oxidative stress during that time, but he studied mostly rancidity. you know, basically meat or butter getting rotten, okay?

Oils, they react with oxygen. Okay, that's fine. What are you looking at when you look at rancidity? You're looking at a dead piece of meat or a piece of butter.

It's not living. The thing about that became more clear, and I wrote several articles that people said were ahead, a little bit ahead of other people, because I was trying to understand why in Alzheimer's disease we found all this oxidative damage and it was in cells that were still going to exist for another 20 or 30 years had the people lived.

So we came up with this idea that basically oxidative stress is basically a homeostatic. issue for chronic conditions. In other words, if you get hit on the head or you have an acute problems, yeah, oxidative stress occurs and you're like the rusty nail and the outcome is you may die.

But if you're aging, you know you're going to have more of this change every year because your underlying conditions are going to get worse. Maybe you exercise and you reset your clock a little bit or you change diet, but you're still getting older.

But in any case, So we came up with this idea that oxidative stress and damage was not necessarily deleterious. Is that buried in all of our papers? Not so clearly, because it's easier to write about oxidative damage and it's detrimental.

But we really don't know what it is. And I think that's the same thing for tau if it's spreading. Interesting. How do we know what it means? Well, we take it away and see what happens, right?

And then you mentioned earlier about synapse changes. So, you know, everyone talks about this synapse loss. There's very poor demonstration of synapse loss in Alzheimer's disease, extremely poor.

We completed a study. It doesn't directly address synapse loss because we didn't do the morphometry in that way. But the original studies were done by Stephen Scheff.

who is currently at the University of Kentucky as an emeritus faculty, and he analyzed synapse density in Alzheimer's disease and by electron microscopy.

Journal of Alzheimer's Disease and Scientific Rigor

He did not find much of a change. The change that was noted was changes in synaptic vesicles by Robert Terry and Eliza Moslia, whose name is mentioned prominently in this book.

He, Moslia, noted that there was changes in synaptomycin. But synaptomycin is not equivalent to synapses. It's equivalent to synaptic vesicles. They're two different things.

So in this study we published a couple of years ago, we did electromicroscopy with morphometry, but not for synapse density, but looking at structures of synapses.

And the vesicles are completely different in Alzheimer's disease versus controls. They're pushed away from the active zone, there are less of them, and they correlate with the changes in mitochondria, suggesting that the big change is synapse dysfunction.

and synapse abnormality, not synapse loss. And this comes back to actually the same thing for neuronal loss. Bob Terry had demonstrated that during the early 80s, late 70s, that there was no correlation of neuronal loss to Alzheimer disease and cognitive change.

That doesn't mean that people who have Alzheimer's disease, of course they have more neurons loss, but it's not correlated strongly. What was correlated…

With the cognitive change. Correct. No correlation. Flax were weakly correlated, tangles were somewhat correlated, and this synaptophysin was highly correlated.

So it's about the health of the neuron. It's not the neuron being there or not there. That you got it exactly. And it's not about the synapse being there or not there.

It's about the health of the synapse and the health of the neuron. Correct. Totally. In fact, we, Mark Smith and myself, who played a major role. Mark Smith was a close collaborator of mine who unfortunately died over a decade ago.

We reckon that the neurons were in the hibernated state. which now in current vernacular they call senescence cells. So this is more in a theoretical.

Have we written anything like this? Close, but never exactly. We thought that the neurons, well, I wrote something over two decades ago. I said the neurons have a choice in death.

That people are always talking about neurons dying, but most of those ideas stem from studying cells that are more disposable. If you're looking at liver cells, hepatocytes are pretty much near identical.

So if you had the chance of the hepatocyte becoming a tumor, you would rather it died. But in the case of a neuron, you really don't want it to die because loss of a neuron has loss of function.

And further, mature neurons do not form tumors. It's stem cells related to them. So mature neurons are set like cells have a choice. They could be, let's die if we have a defect or let's not die.

And I think that that's the way neurons are set. They're set, don't die, don't die, don't die. So don't die has a consequence because the consequence is that you'll have to move all of your metabolism to surviving and you give up functioning.

Now, is there data to show that these senescent cells? Is there data for what I'm saying? Not great. Can they come out of senescence? I think that there is, but the current, this isn't my work, but others.

Most people are trying to kill senescent cells. We want people talking about fasting and getting rid of senescent cells throughout the body by basically starving them.

Yeah, but think about this, that again, if you're dealing with skin cells or liver cells, that's a good thing. How is that useful for neurons in the brain?

Every time you lose neurons, you lose function. My brain is shifting and how I'm imagining what we're doing is essentially like resuscitation of the neurons is our goal.

Correct. But to do so, you have to understand why they went into this state. Right. Because what I view is that they moved to a state where they are not going to die.

They're resisting. Of course, they fail and they die, but they've moved to a state. And to address this type of problem, we studied Arctic squirrels. And why we did that is the Arctic squirrels in Alaska lowered their metabolism to essentially zero during the winter.

They let allow themselves to cool down to minus three. And during that time, we found that the neurons cannot be killed. When they're running around like normal ground squirrels, they're like rats.

The same thing, neurons can die. So is that relevant? I think partially relevant. Number one, the squirrel does this during its whole life. We're only doing this in studying when people are post-reproductive.

There's not a huge amount of selection. So I view that this is a change that's occurring that's related to programs when most of selection is pre-reproductive, period.

Right? If you don't live past 20 or sometime like that, you're not going to have any children, your genes are not going to go forward. If you have a problem when you're 55, the impact is much smaller.

It's not zero, but it's not at the same level. So I view that using programs, so when you're talking about these children, when is the time of greatest cell death in the brain?

Childhood. Right, because the neurons that don't correct correctly have to die. In that case, actively die. So how does that play out in Alzheimer's disease?

I think we're reusing a lot of programs that were important. when they are evolutionarily really important. But we don't see them that way. So can these senescent cells come back?

And then I've had discussions with others who believe that… Number one, all of the cells in the brain, all of the parameter cells, all show the same change.

So when I look at oxidative damage in the hippocampus or something like that, all of the neurons look alike, whether they have a tangle in them or not.

And in fact, if they have a tangle, they have less oxidative damage. So if you're going to try to remove the cells, you're going to have the brain go to mush, which is what we argued in the idea of apoptosis.

that the idea that apoptosis, classic apoptosis was important in the brain, Mark Smith and I calculated that you'd rarely see it. The amount of neuronal loss is so small and apoptosis only usually considered to take less than a day.

You should see like one in 10,000 cells showing this. So apoptosis is planned cell death. It's a purposeful thing. Correct. And that doesn't mean it doesn't occur, but there's no demonstration of it.

So cells, neurons that have tau tangles, can those become untangled or can the axon be fixed so the cell becomes functional again? Well, I don't think we know that.

Okay. I don't think we know that. And even along that line, the tangle itself has even been less carefully analyzed than the plaque. Because if you isolate tangles from the brain, which is not difficult to do, not to purity, but least highly enriched, they have different chemical properties than the type of parahelical filaments that now everybody uses for their studies.

The ones that are used for the studies are soluble in detergents. The ones that are in Viva are totally insoluble in almost everything. I mean, the only thing I found that got them in the solution was high pH, like high sodium hydroxide, or extremely strong protease treatment.

So some of that comes down to convenience. There was a big transition in the 90s, early 90s, in which Sharon Greenberg came up with an isolation technique for a filament that looked quite similar to those making up

neurofibrillary tangles.

But it has different properties chemically. Now, when we've analyzed plaques, okay, so tangles have never been really analyzed biochemically. I mean, everybody will disagree with that statement, but it's true.

The plaques also were super complicated because we did mass spectrometry analysis of the components of pure plaques, and they contain many, many different components other than just amyloid.

So these are very complicated structures containing lots of other components, some of which probably are important, some of which are just happen to be randomly there.

But how those interact with cells is probably far more complex. You mentioned that you've been at this for 50 years studying oxidative stress. You are not a spring chicken, but I am curious.

Don't go into this. Well, I'm curious. With your experience and your research, with what you've learned, what are you doing personally to protect your own brain health and your body in general as you age?

Oh, my wife says that I don't keep any of the advice I give to other people. But what do I do? What are your recommendations? Well, no, I will say, I walk our dogs at least three miles a day.

OK, so that's one. Now, is it a brisk walk? Well, we live in the hill country, so I'm going up and down hills. I take supplements, even though I know that supplements may not be that great.

What are you taking? Oh, multivitamin, fish oil, vitamin D. I take the mixture that's related to ice. So it contains vitamin E and carotenoids. And what else?

I try to keep myself non-stressed. I think I do better than I used to do. And do I have a meaning for life? I like my students. I love doing research.

I love my family. So I at least come close to the four things. I don't know if I go to the Bredesen level of 36 things. You know, I was surprised that you didn't mention sleep.

Oh, yeah, yeah, yeah. No, I do make an effort to sleep seven plus hours a night, usually eight. But I keep a little bit of erratic hours. I generally stay up past midnight.

and I wake up, I don't know, around 7.30 or 8. During the summer, I can come in. Well, I did a webinar this morning at 9. So anyway, then that case, I came to work probably at 10.30 or 11 because it was after that event.

But anyway, I try to sleep every night. In the past, that wouldn't have been true. I would have cut down.

Tau, Oxidative Stress, and Brain Aging

And I do agree that sleep is important. Based upon your reading of the research, what do you like as far as food, both foods that are great for the brain and foods to avoid?

Well, again, my wife wouldn't agree. I drink wine, red wine, and I am Portuguese, so I try to only drink Portuguese red wine. Olive oil, Portuguese olive oil, of course.

Fish, I probably eat fish, Probably four days a week. No, I'm not conscious about which fish. I mean, you've studied the effect of metals on the brain.

Well, metals are more complicated than having too much metals. It's the same thing as oxidative stress, is that you really don't understand why they're there.

So, you know, some companies have tried to reduce metals as a therapeutic venture. I think the metals, our

publications in the past have dealt with the issues of amyloid beta binding copper and redox suppressing it.

Copper can catalyze oxidative damage all by itself. When amyloid binds to it, it blocks that. Okay, we published that, but I didn't like that answer. Okay, I thought it was incomplete.

And why I thought it was incomplete is because that is a stoichiometric effect. And I was convinced that a catalytic effect would be more important. And why I thought so is we had published at the same time that the metals associated with plaques and tangles had fewer oxidase activity.

That is the ability to change iron redox state. And that's usually an important element of controlling oxidase stress. So I thought at that point, which was 1997, that it was related to iron, and we published that in PNAS, Proceedings of the National Academy of Sciences.

And we did everything to rule out copper at our understanding at that point. Not happy with that conclusion, I kept trying to figure out how to do the study better.

And we've done much more about it. So now we understood that the iron was not associated directly with the amyloid deposits and not bound directly. A lot of it was present as magnetite crystals.

And we directly determined that magnetite crystals and that they had magnetic properties. They were not magnetic, but they were superparamagnetic. And then in a more Recent studies over the last couple years collaborating with Joanna Collingwood in the UK, we demonstrated directly the redox state of the metals.

And this is something I was really obsessed with, well, at least for 20 years, the magnetic properties and the redox state. Why? Because knowing there were redox pairs would show that it was catalytic.

So I wanted to understand if there was copper one. And copper one is inherently unstable. I know that's super esoteric, but in order to catalyze the reaction, you have to transfer electrons.

So in those studies, we found something way beyond that. So we found copper one, we found copper two, we found iron two, iron three, but we found the dominant form of the metals was metallic.

Metallic. iron zero, and copper zero. And why was that bizarre? Because neither has ever been determined in the human body prior to our studies. Ever.

Not even close. Copper zero has been found in bacteria, A living copper mines, as an example. But iron zero doesn't exist on the earth, essentially. You know, iron rusts as soon as it's exposed to oxygen.

And here it was in a plaque and stable. So we confirmed this, even our studies initially were in isolated plaques, but we confirmed the work in tissue that has never been treated or anything done inside two frozen sections with no chemical treatment, metallic forms.

Tangles, which we haven't published, do not have iron zero or copper zero. They have metals, but not in the same radar state. So it's again, specific.

You're saying specific to a healthy cell? It's specific to plaques. Oh, to plaques, not to tangles. Not to tangles. Fascinating. And that piece isn't published yet.

In fact, it isn't even submitted. But, so I view that as kind of a control. Yeah. In any case, it says that there's some redox properties that are really quite unusual.

You know, both that it forms, at iron zero and that it's stable because we do not take any special precautions to store them in an oxygen-free environment.

So the specimens are exposed to air and, you know, iron exposed to air. In fact, iron filings will spontaneously

combust when exposed to oxygen under some circumstances.

You know, the only form of iron that was known to ancient man were meteorites. That's how they made, you know, metals and swords, the few that were made to tell you how rare iron was.

There are some ore deposits that apparently have metallic iron, but really, really rare. You know, the way man created iron was to burn it together with charcoal, right?

So the charcoal pulls the oxygen out. So it's not an easy reaction to happen. How does that happen in the human body? We have ideas. you know, reducing power, but I think it relates to mitochondria very much.

So that's one of the main things we're trying to understand. So if we're asking these very basic questions, how are we going to treat the Alzheimer's disease and cure it when we barely understand what the plaque is made of?

We even understand less what the tangle is. We don't understand the role of metals. But as a metals expert, I've got to ask you about mercury because there's mercury in fish.

Well, that's the fishy issue. And I do eat swordfish. You do eat swordfish? Really? Wait a minute. Mind blown. Stop right there. Dr. George Perry eats swordfish.

Now you're not worried about mercury because I love ahi. I also eat that. Should I not be worried about mercury and fish? I don't eat swordfish every day, but I probably eat swordfish once a month.

I do eat fresh tuna. I'm not a big fan of canned tuna. I do eat salmon, canned and fresh. I eat Portuguese sardines. Yes, sorry. I was about to ask sardines.

I love sardines. I'm eating sardines every day. Well, sardines are probably much safer since they're lower in the food chain and you definitely should only eat Portuguese sardines.

Portuguese everything. We got olive oil and evidently red wine is neuroprotective from Portugal. Of course, of course. If you get Torrego Nacional, it has a lot of red color.

Amazing. Dr. Perry, I can't let you go without asking, what do you hope after you're gone? What do you hope your legacy is? Well, you're already getting me dead.

Well, you're on the Think Well, Age Well podcast. And so I want one of the conversations that we talked about, you know, part of aging well is dying well.

And what do you want to be remembered for? What is your whole legacy? You mean in terms of science? Yes, in terms of science and Alzheimer's. You know, I think in terms of Alzheimer's, I think probably the most important thing when they do science is to have a lot of observations.

You know, there's always criticism of descriptive science, but actually I think that for the most part, the best you can do is describe something and describe something well.

So I would like to be remembered that I described a lot of things before other people and had insights before other people. Would I like to have had my work eventually led to a therapeutic or a cure?

Of course, but I'm not sure that'll happen. You know, I think that's something hard to know whether it will happen. But in terms of my descriptions of oxidative stress, vascular changes, origin of plaques, I'm doing work together with Ralph Nixon now.

I also had ideas about how plaques form, which everybody hated, totally. And Dr. Nixon, who's at NYU, came up with an idea that's similar to what I had.

Different, but close enough that I can accept that it's similar enough. And maybe this time it'll be accepted, because there were other people that came up with the same idea.

after me, and they met with even a worse reception than me. So one of the things that probably is the most, I think, beneficial or not beneficial, it's interesting how some ideas take off and some ideas don't, and it's not rational.

I've had ideas that people liked and they took off. That's why I'm highly cited. And I've had other ideas that I think were equally good that no one liked.

And they can never tell me why, which I think is a fault of science. Sometimes I'll have ideas that people say, well, it's clearly is wrong. And I said, well, if you present a wrong idea to me, I get super excited because then I can write a commentary about how stupid the person is.

And I've done that. Uh, several times and I get really excited about it. When you instead just dismiss things, I think it's really improper. So I don't dismiss that amylose is not important.

And further, did I buy the amylo cascade initially? I thought it was reasonable. I mean, I adopt everybody's ideas. Then I look, how do they fit in with what I know from other people or myself?

And I decide my own path. I think there's too much people wanting to be self-reinforced in science. And that is, it's not that much different than high school.

That in high school, you know, you had the people on the football team, you had the cheerleaders, you had the nerds, you had the weirdos. And what group were you in?

I don't know, certainly not the football and the cheerleaders, probably the nerds, but certainly not in the popular group. And I see that in meetings, people want to be popular.

By the way, I'm not against being popular, but I'm not willing to pay. Yeah. It is useful to be popular. It's useful to be rich. It's useful to be attractive.

These are helpful things. All things. Yeah. But you know what? You can't be all of them. They all have a cost. And whether I'd like it to be that I actually tried finding the truth.

That's what I tried all the time, to find things that would stand the test of time and be true. Regardless of their popularity. Popularity is a secondary feature.

A secondary feature.

Personal Habits, Legacy, and Closing Remarks

And I'm popular among the people that come to me. Anyway, and the other people that I'm not popular with, so on. Well, we're in your fan club. We like you.

Oh, thank you very much. Dr. Perry, I just want to acknowledge how much you've contributed to my personal understanding of Alzheimer's disease and my clinical work, and then, of course, to my profession, creating a venue where my work could be published, my research could be published.

And so I cannot thank you enough for that and generally to your contributions to science and our understanding of the disease. So thank you. And thank you also for your time today.

It's really an honor and a privilege to have you here. You said that perfectly, Dr. Sanders. Thank you for publishing my research and thank you for questioning the status quo in science, which is I think what good science is.

It's questioning what is and for having such rigorous standards in your journal and for creating a journal. I have this

running joke. People will say, my doctor says there's nothing to do about Alzheimer's.

I said, well, what do you think the Journal of Alzheimer's is about? Do you think we just publish articles that says nothing to do and every month is the same issue that there's nothing to do about Alzheimer's?

Is that what you think we're doing? So I love the journal that you created and I so appreciate that contribution. There's lots you can do. There's lots you can do even after you have the disease.

You know, maybe the exercise and all this stuff is not going to be as effective, but there's so much work which says that you can have an impact for families, for cost to society.

And further to removing the stigmatism. Yes. Because Alzheimer's, even if you do all of these things, is still likely to be a phase of life for many people.

And what do you do? Do you wall people off, or do you figure out how to integrate them into society as much as possible? And we did that for ancient societies, right?

Grandparents and great-grandparents, if they were still living, played an impact in helping the families. They had a reason to be alive. Meaning. Meaning.

And we've removed a lot of that from modern society, and we probably can't go back. But there can be new ways to do that. And all of those things can actually lower the cost.

to society. And I think that's an important element of lowering the cost, because otherwise it's going to be a tremendous burden, which it shouldn't be.

And we shouldn't view it as a burden if they were more integrated. I agree more. Well, Dr. Perry, don't forget to tell your family that we think you're wonderful.

Are we calling them after? Do we need to call your wife? Yes, you should call my wife or send her an email or something. We can sing your praises and then you can tell her how…

Why you're late for dinner. Yes, exactly. Yeah, no, I've been getting a few messages there. She usually calls me at… See, it's only a few minutes. She usually calls me around five.

Why am I not leaving? And we can see the clock behind you. It's 5, 10 central time. Oh, yes, exactly. I have clocks everywhere. I tend not to be punctual, but I have, let's see, my phone, a clock right up there, another one up there.

That won't be part of your legacy, but tell your wife you're late to dinner today because we're big fans and we were hoping to extract some wisdom and just some of your experience from you because it's so inspiring, it's so hopeful, and you're just doing some incredible work.

So thank you again for being here. Thank you so much. Thank you very much, Heather. It's great to meet both of you. 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.

Thank you for tuning in to Doctor Talks. We hope today's episode has enlightened and inspired you on your path to optimal health. Each day is a new opportunity to make choices that empower your well-being.

For more insights and strategies, subscribe to our podcast and visit our website, www.doctortalks.com. Stay

connected, stay healthy, and join us next time on Doctor Talks.

Real talks from real doctors on the issues that matter to you most.