CUTTING EDGE Health

Welcome to the *Cutting Edge Health* podcast with Jane Rogers, where we discuss science to help prevent cognitive decline.

Jane Rogers: Why don't we have a cure yet for Alzheimer's? We've been studying it long enough, clinical trials have been tragically disappointing, and the Feds are funding research to the tune of $3 billion a year yet we're coming up empty-handed. Why? At the University of Pittsburgh Medical School, there's a lab researching the causes of Alzheimer's. Dr. Karl Herrup is an investigator there. He's a professor of neurobiology and a longtime well-respected researcher widely known in the field. In his new book *How Not to Study a Disease: The Story of Alzheimer's*, he speaks out about why we don't have a cure yet and what's ahead. Welcome to *Cutting Edge Health.* We're so glad you're here, Dr. Herrup, thank you.

Dr. Karl Herrup: It's a pleasure to be here.

Jane: You have been a researcher of Alzheimer's for how many decades has it been?

Dr. Herrup: I usually don't divulge that information, but I've been working in the field since 1992 when I joined the Alzheimer's Center at Case Western Reserve University.

Jane: Well, thank you for your years of service trying to find a cure. Thank you very much. I know you've worked hard. My father, when he was first diagnosed with mild cognitive impairment, I was in my 30s. I thought, "You know what, I'm not going to have to worry about this. We're going to find a cure for it long before I have to start worrying about it." Now, I'm 60, had my own memory issues at the same time my father did at 54, and we are still in a position that we're looking for the answer. Tell me about the process that's gotten you here, and with 20-20 hindsight, what have you done right and what would you do differently?

Dr. Herrup: Well, let me just start by saying I resonate with your personal example because I do remember when I first got into this game that I was assuring my kids that, "Look, this is a long process, and I may not be able to prevent my own Alzheimer's, but I'm sure I'll be able to prevent yours." Fast forward to 2022, I'm not so sure about that statement anymore. In that way, our journeys have been similar. What have I done right? What have I done wrong?

I feel the right part of it has been to dive into this disease and its biology in all of its complexity and rather to ignore the complexity, to understand it as actually a signature of the disease. Maybe if I've done anything wrong, it would have been to, I think, sit too quietly, too long, about insisting that the field be more rigorous in its own investigation of

what the causes of the disease are, and so, perhaps, jostle people off a misguided path a little earlier.

Jane: When you say a misguided path, I was reading in your book that in 2002, there was a dye, the compound B, Pittsburgh compound B that you would use in a PET scan, and it would identify amyloids in the brain. It identified that 30% of people, older folks, had amyloid in the brain, but they were showing no signs of cognitive impairment at all. That shows the amyloid hypothesis, the cascade that we have been pursuing for so long as the problem with Alzheimer's, to get rid of the amyloid plaques Alzheimer's will be done, is not right because normal people have amyloid.

Dr. Herrup: Well, there you go using logic again. The problem, I think, we face is that your reaction is a perfectly natural one. In fact, it's the one that I think more than any other got me started, what I think many of my colleagues in the field consider a quixotic approach to the disease. Yes, I think that's perfectly true that if you have a brain with sufficient plaque density, amyloid deposits to be diagnosed as Alzheimer's but you're cognitively normal and going about your life, it's really, really hard logically to say you have a disease.

Yet, what the partisans of the amyloid hypothesis have done is they've turned that weakness into a strength and said, "Well, what that really means is that these people have Alzheimer's disease. They just haven't shown symptoms yet." It's really hard to make that make sense, has been my contention all along, and then we get into the weeds. Yes, I think you're absolutely right. The presence of that group of people, the 30% of cognitively normal individuals with amyloid burdens that look for all the world like they belong in the brain of an Alzheimer's patient, it just totally undercuts the hypothesis.

Jane: You said you've been quiet for too long. What are you wanting to say?

Dr. Herrup: Well, the book was my cri de coeur as it were. I think what I really wanted to say is that, "Look, this is a complex problem and we do ourselves as researchers and the public in general, a great disservice if we try and make it simple when it's not." It's an extraordinarily prevalent disease. Once we reach the age of 85, the odds are around 30% to 50% that we will have some symptoms of the disease. That's simply extraordinary. That's almost like saying having Alzheimer's is part of being human. Yes, we need to do better.

Jane: Tell me, one of the ways we went wrong was chasing this amyloid. In doing that, we ignored some of the other complex factors that are leading to cognitive decline. A lot of that was a funding problem, right?

Dr. Herrup: It became a funding problem, yes. As the amyloid partisans gained more and more ascendancy and power in the field, it became easier and easier for grants that didn't embrace that view of the disease to be turned down as not worthy. The same with publication of manuscripts. That, as I think you're hinting and I would certainly emphasize, was and is a huge problem for the field.

Jane: Looking back still, and then we'll look forward, and, hopefully, we'll see some light and some hope, were there some alternatives to treatment that now you see, "Oh, my gosh," when you're lying awake at night, thinking, "What could we have done differently?" Are there some alternatives you really wish you would have bird dogged 15 years ago?

Dr. Herrup: That's an excellent question that I can't answer. The reason I can't answer it is, as a basic scientist, I would want the underlying biology to make a recommendation to my clinical friends to please try this. We've been so blocked in our ability to get at that basic science that I find it really difficult to offer advice to my clinical friends. I think the best advice actually is that looking back, I don't want to oversell it, but it's almost like, "Your mother was right. Eat right, exercise, do things that are generally healthy." As far as we know, that, ironically, is one of the best things you can do to prevent Alzheimer's disease.

Avoiding the sugars and fats that lead to adult-onset diabetes, that would be a huge benefit to prevent Alzheimer's. Not to prevent, but to lower the risk of Alzheimer's disease. The more we learn, the more we come to understand that what's good for your heart is good for your brain, so keep your blood pressure under control. This is where exercise comes in. Cardiovascular fitness. These are really simple things and, yet, as we learn more and more, it seems to be that these simple things are the ones with the largest effect. I could stop there or we could go on a rant about the pharmaceutical industry and simple things actually don't fit their business model, but for now, I'll stop.

Jane: [laughs] I am assuming then the new Alzheimer's drug that was just approved by the FDA is something that you're-- I shouldn't prejudice that statement. I should just ask you, what do you think of it?

Dr. Herrup: Go ahead and prejudge it because, no, I'm not a big fan. Well, certainly on a theoretical basis, as a scientist, I had very little hope for the success of the strategy, which is the idea that removing amyloid from the brain was going to halt the progress of the disease. I think quite apart from that, what is more irritating to me and I think has caused more of the controversy in the field is the way in which the approval process went down. There was too much industry regulation feathering each other's nest than I think is healthy. The drug should never have been approved on the evidence that the

FDA had before it. I think we will live with the consequences of that bad decision for quite a while.

Jane: You are one of the preeminent researchers of Alzheimer's. I'm wondering, do you see hope? Are your colleagues reading your book and are they listening and learning from the problems of the research in the past?

Dr. Herrup: Let's see. Those are two really separate questions. Are my colleagues reading my book? Yes, I heard mostly from younger people how pleased they are that someone has finally stood up and said all this in public. From my older colleagues I think I had the same reaction that I talk about in the book with respect to the other non-amyloid hypotheses which is complete silence. I guess in retrospect I should have expected that but the silence has been deafening. To get to your first question and maybe this will even seem as a paradox, my answer is yes, I'm optimistic.

I do think that the string of clinical trial failures that has beset the field over the last, let's say, decade has really laid the groundwork for opening up alternatives in research. I threw a few ideas out in the book. There are many many more that could be undertaken but because of that newfound openness to alternative ideas, I see it both in the basic research but also in the clinical space. That makes me quite optimistic. I've been asked if I'll give a timeline. I won't. I do feel that the field is changing and for the better.

Jane: Your lab at the University of Pittsburgh Medical School, you're gutsy. You've written this book. You're saying we need to look at new things. What are you pushing your lab to do now? What are your dreams for this lab?

Dr. Herrup: I've said this to others. In many ways because of my perspective on Alzheimer's disease it has enabled one of my worst characteristics as a scientist which is I'm too curious and I want to try too many things. In fact I believe I'm probably doing--

Jane: That's a good thing, Dr. Herrup. That's good.

Dr. Herrup: If you've got a team of 100 people, yes, it's a good thing. You can afford it. But I have a small lab and like to do research that way. To be serious for a moment, I'm very interested in the role of DNA damage. Another way of saying that is the flip side of that which is what we call genomic integrity. That is to say keeping the DNA of your genome intact for as long as possible. I'm interested in that in a theoretical way because we have a lot of really good data that says that this accumulating damage in our cells' genomes really is a driver of the aging process. Since age is the critical risk factor for Alzheimer's disease, young people don't get it.

I feel like the study of that genomic integrity issue is really important and so I'm on it. The specific angle that I'm on right now is the linkage between that and inflammation. We're working on the connection between how the natural accumulation of DNA damage with age leads to a natural accumulation of a slow simmering inflammation. What's attractive to me about that as a basic scientist is that it's in that connection that we can, maybe, find what are known as druggable targets. In other words, points of intervention where we can actually uncouple the processes from each other and maybe make a difference in Alzheimer's disease.

Jane: So important. My inflammatory markers have always been three to four times what they're supposed to be. I have tried and tried and tried to get them down. There's some research now coming out of Japan that I found really exciting. There's a vaccine that they just developed to get rid of the sensient cells. Those zombie cells they call them. That can really hurt your DNA. Is this on the right path?

Dr. Herrup: Yes, it is and senescence as a cellular phenomenon is on my radar as well. I think you nailed it there. It fits right into this linkage between DNA damage and inflammation. I'm using information in the broadest sense and I think what the studies like the Japanese study show is that one of the problems with senescence is it generates an inflammatory-like environment. It goes by the name SASP for Senescence-Associated Secretory Phenotype. The words aren't important but what it means is that when cells senesce they misbehave and they begin to put substances into their environment, which means into our brains, that are bad for the healthy cells around them.

Jane: You are using mice in your research?

Dr. Herrup: In our experimental work we use mice as our research tool. We also use cell lines when we can in culture. We almost always try and validate what we find in our experimental systems in human material histological work on material from human brains of individuals who've died either with Alzheimer's disease or for other causes.

Jane: You've told us what you're working on now. You've told us what your concerns are in the past. You go to a party, let's say. I've been getting this all the time from my friends since I started this podcast. I'm having memory loss. What should I do? What should I do? I'm sure you get it all the time.

Dr. Herrup: I do.

Jane: You want to help. You want to tell these people we've talked about some things you can do. We've talked about eating well and keeping your blood sugar down and exercising. Is there anything else to lower inflammation, to fight aging, that you might

say, "You know what, people our age have got to consider that because research is going to help maybe our children but it's not going to help us."

Dr. Herrup: Yes, I've gone as far as I'm comfortable going with things that I would say at a party, if you know what I mean. The inflammation angle that we've been talking about is a tough nut to crack. There's data that suggest that if you take very high doses of anti-inflammatories you can lower your risk but the doses are so high that the risk of damage to your intestines vastly exceeds any benefit you might get. Of course, the other problem is the prospective trials where they've tried to use anti-inflammatories as therapies have failed. They've not been as extensive as the amyloid trials but it just doesn't seem like we've got the right entree.

I'm straying from your question back into the basic science but I would tie it back to the point you were making about the senescence as one of the villains that is tying our brain to the railroad track. The inflammation that is created, the inflammatory process that is created by senescence is actually quite different from the inflammation that's created by cutting yourself and getting infected in your skin. There's the hope in my mind that taking different anti-inflammatory strategies than the ones that have been used might actually end up being effective. Targeting the senescence induced inflammation rather than a typical bacterial induced inflation.

Jane: Anti-aging. If we can prevent aging, we can prevent age-related disease. There have been a host of things that have come out in the last year to help fight aging. One of them is metformin to make sure you lower your blood sugar. Studies are showing that someone on metformin seems to have more cognitive abilities even with diabetes than someone not even taking metformin and no diabetes. There's rapamycin which, supposedly, helps anti-aging. Do we need to fight aging to prevent age-related diseases?

Dr. Herrup: The short answer is yes, but let me give a longer answer. I think the idea of fighting aging is where I want to dive in a bit. I don't think it's something we can fight. I do feel it's baked into our biological cake but what we can do is work with it and control its more serious negative effects. That is certainly in essence what we've been talking about when we talk about senescence and avoiding it. Avoiding aging is not an option.

Jane: It happens.

Dr. Herrup: Death is not optional. I don't mean to be morbid about it but I do think we can vastly improve what's known as health span as opposed to lifespan. How long do we remain at peak performance or at least good performance as the natural aging process takes its toll. That's certainly the way I approach the problems related to Alzheimer's disease. The goal is to keep the brain going and put the problem of aging

on the kidney doctors and the bone doctors and let them deal with people with healthy intact brains.

Jane: That's a really good thought. Increase our health span. It's so important. We don't want those years like my mother right now in memory care. We want to extend that. Dr. Herrup, what else do you want to tell us? I know it is important for you to talk with people like me who are lay people in the field and not scientists. Is there anything else that you haven't covered that you'd like to?

Dr. Herrup: I guess if I'm addressing a lay audience such as the people I believe listening now, I just want to start off by thanking you. As a basic researcher I cannot tell you how grateful I am for the support that our community has received over the years as we struggle to understand what's going on with Alzheimer's disease and to untangle the complex biology that makes it a problem. Thank you for that support.

If I could ask one more thing I'd just ask for patience. Our field is struggling right now. It's undergoing a major change in terms of our model of how the disease actually works. It's not going to turn around on a dime. This is something that will take time. I'm not talking about centuries, but we're not going to have a cure by the end of the next quarter for any of the pharmaceutical companies' annual reports. Thank you for your support and patience, please, while we keep working on this problem.

Jane: Dr. Herrup, thank you for that heartfelt. Thank you. Thank you also for what you have done to help families like mine all over the world. Appreciate your time-

Dr. Herrup: Thank you.

Jane: -and you have an awesome day.

Dr. Herrup: Will do. You too.