SEAN COLLINS (00:00:06):
It is the Hear Me Now podcast. I'm Sean Collins. Glad you're listening.

(00:00:12):
This is our last episode of 2023, and when we go through our notes and look at the stories that have garnered headlines this past year, the tales of both human achievement and tragedy are writ large. As we debated whether the pandemic was over, ongoing tracking of covid ended in many states and long CO made headlines. Month after month, Oregon became the first state to okay the use of hallucinogenics like psilocybin, and we saw its use in treating complicated grief. The GLP one receptor agonists like Ozempic and Trulicity and BTA are said to change the game in the treatment of obesity, heart and kidney disease and type two diabetes. We saw the mainstream rolling out of artificial intelligence in healthcare. The first use chatbots, RSV treatments became available. The respiratory illness can be deadly in children and older adults, and its treatment has dogged scientists since the sixties. Ongoing deaths from fentanyl and other opioids continued, NARCAN — the overdose reversal drug — was approved for sale over the counter. In the wake of the SARS-CoV-2 pandemic. Chronic organizational stress led to unprecedented burnout and job abandonment by nurses, physicians, and other healthcare professionals. We've seen continued focus on issues of healthcare equity. Gene and cell therapies get closer to the market making CRISPR technology the next medical buzzword. CRISPR is just one technology leading to unprecedented breakthrough treatments for people with sickle cell disease. Roe v. Wade was overturned by the Supreme Court's Dobbs decision inaugurating a new era of debate over access to reproductive healthcare. Pediatric gender dysphoria was legislated in state capitals around the country. And in this year of remarkable advances, perhaps the most noteworthy breakthrough was FDA approval for new treatments for Alzheimer's disease.

(00:02:45):
And Alzheimer's research is the subject of today's program.

We're pleased to welcome two leading Alzheimer's researchers and an author who's been writing about Alzheimer's for the last 20 plus years. Dr. Steven Salloway is founding director of the Memory and Aging Program at Butler Hospital in Providence, Rhode Island, and a professor of psychiatry and human behavior and professor of neurology at the Warren Alpert Medical School of Brown University. Dr. Salloway, it's a pleasure to have you with us. Welcome.

DR STEVEN SALLOWAY (00:03:14):
Thank you, Sean. Appreciate the invitation.

SEAN COLLINS (00:03:17):
Dr. Rudy Tanzi directs the Genetics and Aging Research Unit at Massachusetts General Hospital. Director of the McCance Center for Brain Health at Mass General, Dr. Tanzi is professor of Neurology at Harvard Medical School. Dr. Tanzi, welcome.

DR RUDY TANZI (00:03:35):
Thanks. Pleasure to be here.

SEAN COLLINS (00:03:36):
And David Shank is a national bestselling author of six books, including "The Forgetting — Alzheimer's: A Portrait of An Epidemic." He served as a senior advisor to the Cure Alzheimer's Fund and advised the President's Council on bioethics on dementia related issues. He's also an old friend. David, welcome back to the podcast.

DAVID SHENK (00:04:01):
Such a treat to be back with you, Sean. Thank you.

SEAN COLLINS (00:04:04):
So anyone who's read newspapers has noticed headlines over the past year or so that indicates that there have been what appeared to be remarkable advances in Alzheimer's research. And I want a little bit of a reality check from those of you who are

seasoned researchers here. What should we make of that? Dr. Tanzi, let's start with you there in Boston.

DR RUDY TANZI (00:04:28):
Well, the big advances for many of us who have been convinced that beta amyloid, the material and the plaques in the brains of Alzheimer's patients cause this disease. It's great to see a drug that hits those plaques, hits the amyloid, and it was successful in a clinical trial. The genetics always predicted that the genes that we discovered back in the eighties and nineties all said amyloid causes this disease, but many trials failed that were targeting amyloid. So to have a trial that provided the proof of concept to hitting amyloid is beneficial is just great. It's great for the field. But the problem is, and we can get into this later, hitting amyloid in a patient who's already symptomatic, in my opinion, I'd like to hear Steven's opinion. It's just too late. We got to do better. We need drugs that we are going to be able to use for the masses before they have symptoms. I like to say amyloid should be hitting Alzheimer's the way cholesterol should be hit in heart disease. And we don't diagnose Alzheimer's until the equivalent of with heart disease. You already have congestive heart failure or certainly coronary artery disease, and at that point you wish you took Lipitor or some type of statin cholesterol drug 10 or 20 years before. I think that's how to think about amyloid. Great breakthrough. We still have to do it earlier, so we're going to need safer, more affordable drugs to do it. But this is a great start,

SEAN COLLINS (00:05:55):
Dr. Salloway?

DR STEVEN SALLOWAY (00:05:56):
Yeah, I agree with Rudy. I think we're at a turning point where Alzheimer's will increasingly be viewed as a treatable disease, and this is the first step in that that we can diagnose it increasingly earlier and we can institute treatments, just either slow it down or prevent it. And this is the first one, and Rudy already gave caveats about its limited benefit, but there is a benefit which is good, and we got to do better and we got

to go earlier and we have to have treatments that are more widely available than this. This is going to be challenging to administer to a large number of people and hopefully eventually treatments that are either oral or can be given infrequently to a large number of people without too much expense. So I think we're just at the dawn of a new era

SEAN COLLINS (00:06:55):
That sounds hopeful.

DR STEVEN SALLOWAY (00:06:57):
Finally, I mean, and Rudy and I have met this a long time, we can tie up how many years, how many studies, how many projects.

DR RUDY TANZI (00:07:06):
I guess Steven, there's those folks I know who never were swayed by the media hype that oh, amyloids the wrong target, amyloids not the right thing just because people were debating it. You have to realize the reason why people weren't believing amyloid caused the disease originally because, and again, look at the genetics. The first gene we found, I discovered it as a student along with others when I was at Harvard, that was my PhD thesis. I named it a PP amyloid precursor protein. It's the protein that makes the amyloid. The second two genes, the presenilin where the enzymes that cleave the protein that make the amyloid. The fourth one, a OE, is the protein that declares the amyloid from the brain. Yet given all that evidence, people said, no, it's not amyloid because when they put these genes in mice, the mice didn't make the second pathology that kills the nerve cells, the tangles.

(00:08:04):
They never stopped to think, wait a minute, can mice even make tangles? Guess what? They didn't have the right proteins of this protein called tau to make the tangles. So there was debate for over a decade and a half based on that. Then finally when we created the first human brain organoid of Alzheimer's and put amyloid in with human neurons in a brain-like environment, bang, amyloid tangles. And so I think that to me, I

think we're on the right track now. I think Steven said exactly right. This is the dawn of a neuro error, but we got to do so much better. It's just we have proof of concept. It's a great breakthrough, and I totally agree with Steven. We need small molecules, little white pills you can take in the morning that are immensely cheaper and safer. Safer that we can use the way we use cholesterol drugs or heart disease to prevent Alzheimer's in tens of millions of people in this country right now.

SEAN COLLINS (00:09:03):
Yeah, it's intoxicating to think about a statin approach to being able to stop a disease process that's so damaging and rips so many families apart before it begins. I mean, that's a remarkable dream.

DR STEVEN SALLOWAY (00:09:19):
Well, Sean, it's a requirement because if you really look at the curve for heart disease where we've made great progress in slowing down the impact, the morbidity and mortality, it's from a combination of prevention, statin like drugs and good heart health and good healthy lifestyle, and then acute treatments. When someone does have an occlusion of a coronary artery, we can open it up and we need both. And same thing for Alzheimer's. We got to be able to prevent it early and as Rudy said, this disease goes on for years, decades before their symptoms are really noticeable or persistent and we get a lot of time to intervene and get in there earlier. And so that's our challenge.

SEAN COLLINS (00:10:06):
David Shenk?

DAVID SHENK (00:10:07):
We're listening to two of the great minds in this field and it's just a pleasure to hear this and I can't wait to hear more to kind of put it in layman's terms. As someone who's been following the science from the outside for almost 25 years now, I just want to second and third this thought that we have turned a corner, we've crossed a threshold.

We've had a lot of really brilliant minds working on what may be the most complicated disease ever that human beings have ever faced. There've been a lot of discoveries over the last several decades, but now that we have a couple of drugs that are actually treating the disease, albeit in just tiny, tiny steps it feels like, and because we've had some proof of concept that Rudy started to describe there about amyloid, it feels like for the first time we have the justification to actually have hope that we can stop this disease.

(00:11:26):
And so what I want to explore, at least in part in this conversation is how much hope can we allow ourselves to feel? Can we actually see the end and start to describe what that might look like? And as Steve just suggested, is it two different things? Is it three different things? Is it a dozen different things as we discover this disease? There's a lot of different types of diseases, but let us kind of acknowledge that hope and explore it for ourselves because I think the hope itself gives new energy to the will, the national and international will to stop the disease.

SEAN COLLINS (00:12:07):
Yeah, I think that's a really great tack for us to take in the conversation. So the hope that David's describing Dr. Tanzi, Dr. Salloway, how much hope are we going to allow ourselves to have?

DR RUDY TANZI (00:12:21):
I'm never had more hope on my life. I mean, I worked with a foundation that David's worked with as well, the Cure Alzheimer's Fund, and I had to give a talk to their board this morning, and this was after our researchers really a list of Alzheimer's researchers yesterday had a brainstorming session and one of the things came out of that brainstorming session was so simple, so simply put by Randy Bateman, who's one of the top Alzheimer's researchers at WashU St. Louis. And he said, look, everything I've learned about this disease, and he's been studying the early detection, early biomarkers of this disease, imaging biomarkers for as long as anyone is, the faster you

accumulate amyloid in your brain, the sooner you get Alzheimer's disease. Okay, that's the elephant in the room. And so I wanted to explain this to the board members. So I made some slides this morning to show them or I have a sink overflowing with water, and I said, this is the brain overflowing with amyloid.

(00:13:31):
How did you get there? The tap could have been leaky or the drain could have been clogged. Once that water overflows, what happens? Well in Alzheimer's, the amyloid causes tangles and the house, the water's going to cause electrical short circuits and little baby fires to start to spread, and then those little fires suddenly start engulfing the entire house. That's called neuroinflammation. By the time we diagnose a patient right now, the house is already burning. It's not just a short circuit in the wall. It's not just a bulb that water got into. So just put it in that regard to help patients right now, you've got to put that fire out. But to prevent this disease, you have to go to that sink and make sure that drain is unclogged and make sure that tap isn't leaking. And that's the way we're going to start. I have a drug that turns off the tap is going into clinical trials after 25 years next year. Others have drugs that can more cheaply clear the amyloid than the current antibodies that at least provided proof of concept. So yeah, I'm extremely optimistic about the next five years or so.

DR STEVEN SALLOWAY (00:14:47):
I think the biggest thing we have to do is really Alzheimer's out of the darkness. So there's always been this feeling that Alzheimer's is sort of an inevitable part of aging. There wasn't much you can do about it. There's no urgency for diagnosis. The treatments aren't really meaningful, the ones we've had for a while. And so doctors and many patients and many families have just tried to ignore it and obviously doesn't go away by ignoring it. It's just a major league problem and we've got to bring it out into the light. And then I think that's what some of these breakthroughs. So we talked about the new antibodies that lower amyloid, I think a really exciting development are blood tests that can detect the buildup of plaques and tangles well before symptoms. That's

going to be much easier to administer than pet scans or spinal taps or other tests that are more expensive or invasive or hard to come by.

(00:15:48):
So that's a big breakthrough and those are just coming into the clinic. And the other critical element, and that's why I'm so glad you guys are covering this in this podcast, is getting the public engaged, which I think that's going to happen. I'm not worried about that. The public is really concerned is getting primary care doctors engaged because that's where patients go and that's where they seek advice for their health and they need good advice from their family doctor. And I think I know there are real challenges there because family doctors are so stretched and when you put cognitive difficulties on there, that adds a whole component to a visit that they just don't, are just not budgeted. So we have to figure out how to do it, how to provide the care, but it's critical that primary care doctors and the public, all of us really get engaged. And the only reason we're at this point with these breakthroughs is we've had so many great research. We've had great researchers like Rudy and many others, but we've had thousands and hundreds of thousands of study volunteers around the world who put themselves on the line to test these new development to make these developments possible.

DR RUDY TANZI (00:17:03):
I think Steven's saying early detection, early intervention is the way forward. We can't wait for the brain to deteriorate before we diagnose the disease.

(00:17:11):
David Shenk?

DAVID SHENK (00:17:12):
Yeah, question for Rudy. You're very hopeful about this early intervention. Do you think that we're going to get in some period of time and maybe it'll take years and years to get the right drug that's safe enough or maybe it'll be a handful of different drugs

targeting people who have different chemistry, but will we get to the point where we can actually intervene in enough people using that statin model so that the reality of Alzheimer's that gets to the middle, to the stages of the symptomatic stages, that'll be a rare thing and we won't have to even spend that much energy in treating it. It'll be so rare. Or do you think that we're going to have to put just as much energy always even after we get that drug that does the early intervention into different drugs that attack it at those later stages?

DR RUDY TANZI (00:18:05):
So the current breakthrough with the antibodies, the immunotherapy against amyloid is if that was heart disease, you're waiting to have coronary artery disease and now you're trying to clear the plaque from the arteries, but damage has already been done and is ongoing like inflammation in the heart. So it's good and it's helping, like I said, incrementally, but wouldn't it be nicer if you truly had a statin that never lets you get to the point of coronary artery disease? Nevermind the fact that we don't diagnose the disease today until you of Alzheimer's, until if heart disease, it's the equivalent of congestive heart failure almost. So I mean things are moving on. When I started in this field, I did my first genetic study of Alzheimer's in 1982 and we had nothing, and then we got Aricept and naa and it was better than nothing. At least you're starting to treat the symptoms, you're helping people.

(00:19:06):
And now here's the breakthrough. We have something that at least helps clear the plaque. And so logically you're going to say, well, how about a drug that doesn't let the plaque even get there? And Steven mentioned these biomarkers, the blood-based biomarkers. Yeah, we have blood tests that can tell you you have amyloid in your brain, and I don't know what you say Steven, but some people who study this stuff say that if you ask how many people in this country have amyloid in their brain right now but don't yet have symptoms of Alzheimer's disease, I've heard estimates anywhere from 10 million to 40 million. So that's a lot of people that you're going to want to start treating with. Early detection, early intervention, I want to treat before they have the

amyloid that's current art artery disease in heart disease terms. And Randy Bateman says he has biomarkers.

(00:19:55):
He can use the current biomarkers to tell you who's five years away from plaques. So you don't have by imaging of blood test, brain imaging or blood test, you don't have amyloid yet, but you're on your way. And so the people with two copies of a POE four or the early onset familial mutations or even down syndrome would have an extra copy of the amyloid gene. They you start treating, you don't wait, you start treating. So if you have a drug that can turn off the tap, turn down the amyloid production before the brain's full of amyloid, that's the next step. So one next step is try to get rid of the amyloid more safely and affordably than the antibodies. But even going beyond that, turning off that top stop the amyloid from even accumulating early on and then we're really put a dent in this disease, we have a chance to really almost eradicate it.

DAVID SHENK (00:20:52):
Steve, same question to you. And just to rephrase it, do you allow yourself to be so hopeful that we can get safe enough, good enough drugs that target the right people that can get in there early enough such that we could actually effectively eliminate the disease before it starts so that the actual symptomatic Alzheimer's disease at some point in our future can be just a very, very rare occurrence?

DR STEVEN SALLOWAY (00:21:19):
I don't think we're going to answer your question, Dave. I don't think we're going to eliminate Alzheimer's like polio or smallpox where actually it's been eradicated. But I think I totally agree with what Rudy just said, that I can envision treatments that are vaccines against amyloid and tau that could be given just a couple of times and perhaps together it's someone either in the early accumulation stage or as Rudy says, if we have biomarkers that can predict who is going to develop amyloid just on the verge even better and then block it, we're going to make a huge impact. So you're not going to see the millions of people, and we're talking about tens of millions of people

worldwide who are affected by this disease. We can knock that down substantially and also decrease the morbidity of it so that if you do get it, it's a milder form, it's later, it just has less impact.

(00:22:19):
I don't think we can eradicate it, but we can make a huge difference. And then I think Rudy's hinting at oral agents now that'd be great. And that's possible. So far, the ones we've tried, the beta secretase inhibitors have had problems that decreased the production of the toxic forms of amyloid into the plaques and they've actually had worse outcomes cognitively. So we've been a little stymied there, but I think we will come up with something eventually in the oral, they'll be easier to administer orally that can have an impact. And I see us soon, sooner rather than later, is finding combination of treatments that target, as you said, different component. Everyone has their own phenotype, so depending on what are the components of that person's illness, you can target those more specifically. And target inflammation may be if one of these drugs that works for diabetes and also decreases inflammation like ozempic, something like that, where to be effective, there is a trial for Alzheimer's disease. That would be fantastic and that could be a combination treatment.

DR RUDY TANZI (00:23:33):
The beta secretase inhibitors you brought up failed because of safety. There was a meeting about this recently in New York, New York Academy of Sciences, and there was some consensus including by Bob Vassar who discovered beta secretase itself that it's becoming increasingly clear that what makes up the amyloid, the amyloid beta protein has roles in the brain. One is to help control the firing of nerve cells. The other is to act as we showed as a host defense peptide. So a lot of us think that just stopping its production was too harsh. You need some of it. So what my colleague, my late colleague Steve Wagner and I did 25 years ago was we invented something called gamma secretase modulators. So to make amyloid beta protein from its substrate protein, you need beta secretase clips. The first clip, gamma secretase is the second

clip and the Alzheimer genes called the presenilin that cause early onset familial Alzheimer's make the gamma secretase.

(00:24:36):
It makes the second clip. And when they try to inhibit that with a sledgehammer, people almost died. That was really bad. Same thing. So we said, let's learn from the genetics. Let's see what the mutations in the genes for gamma secretase, the ILSs. Let's see what they do. And let's just reverse that and I won't get into the details, but by reversing that, and it took 25 years and about $30 million from cure Alzheimer's fund and the NIH to get to this point, we have a drug that acts like the Juul, a screwdriver that doesn't bash the enzyme, but tweaks it and gets it to create the right forms of the amyloid beta protein that prevent amyloid formation rather than drive it. Meanwhile, you're not hitting the enzyme with a sledgehammer so you don't make people sick. So that's the drug. It took 25 years I had to start a company to develop the respite because to put in the application to the FDA to get it into trials, they said we want a corporate sponsor for that.

(00:25:41):
So I started a small company a year ago and now we're waiting for the FDA to give us the approval to start our trial. We're hoping to get our first phase one safety trials going in March or April, and if those are successful, we're going to come to you. Steven say, let's go. Let's go in Rhode Island, my home state and start doing the efficacy trials and treat patients. But here what we're going to do is we want to show it can be the statin of Alzheimer's, something you take even before the brain has amyloid. And so that's going to be new for the FDA to deal with.

DR STEVEN SALLOWAY (00:26:13):
So I hope that Rudy's drug will be successful and we'd be happy to test it if it looks good. And whether it's that one or another one, I think we will ultimately be successful in that strategy. It's going to take some tweak. Rudy laid out the way has not been straightforward. We've tried with what seemed to make sense, but so far has not been,

we haven't been able to carry it forward. But I think Rudy's strategy is good and there'll be others as well.

DAVID SHENK (00:26:43):
If I can jump in with a follow up there. So you guys have so clearly outlined this amyloid strategy and how hopeful we all are in different degrees toward that. I wonder if you could give us, now take a step back and give us a lay of the land of the energy that's going into the whole picture and into some of these other things. The inflammation piece, the tau tangle piece, which happens later in the disease. And once those are in there, there's just real destruction happening in the brain and whether you think, so question part A of the question is how much energy and proportion and money is going into those other two sectors and are they the right portions as far as you're concerned? In other words, is it 60% now going to the amyloid thing and that sounds about right and another 30 to T and another, what's left 10% to inflammation or is it something else and is it right or wrong? And do we need to rejigger those portions based on what we now know?

DR RUDY TANZI (00:27:50):
Steven can comment on the pharmaceutical side because he's as stick as anybody into the trials, but on the research side, I think the NIH has done a good job of dividing money between amyloid and tangles. And remember amyloid as its community is making tangles pretty quickly. Where we were lagging was on what really causes the most nerve cell death and loss of synapses as the amyloid tangles accumulate, which is neuroinflammation chronic inflammation in the brain, but we didn't know what to target. And the cure Alzheimer's fund had funded this Alzheimer's genome project that I was running in an oh eight. We found this gene called CD 33 as an Alzheimer's gene. We didn't know what it was and Time Magazine calls it a top 10 medical breakthrough of oh eight. And we were laughing like we don't even know what this gene does. Then we figured out that this gene turns on the neuroinflammation, it's the on switch and it implicated a cell in the brain called the microglial cell.

(00:28:53):
And since then we found we and others, the royal, we have found over 60 Alzheimer genes that control microglial cells and whether they're going to cause chronic inflammation. So now we have targets for the first time, CD 33, TREM two, ship one, et cetera, et cetera. So the pharma companies are jumping on these and the NIH is making a big push because if you want to help a patient who's symptomatic where the fire is blazing, you got to put out the fire and that fire is chronic inflammation. I think that you have to find the targets first, and I think now we're there. So you're going to see more of an equal split in the funding.

SEAN COLLINS (00:29:33):
Dr. Tanzi, does that mean that a technique like CRISPR is going to become useful in genes that people have?

DR RUDY TANZI (00:29:43):
Well, it's one thing to do that in sickle cell anemia, which we just saw the approvals for. It's more straightforward, you put it in the blood, but trying to edit all the cells that you have to edit at once and do that safely without any side effects in the brain, it's a lofty goal. But I still think we're pretty a few steps away from that. It'd be great, but I think we're still far away from it. I dunno. Steven probably has an opinion on that.

DR STEVEN SALLOWAY (00:30:15):
Well, just to answer your first question and the second question there is diversification. We're going to need open-minded science and discovery and that focuses on different components of the disease. And if you look at the pharmaceutical trials and the NIH, it is a diverse portfolio. Amyloid is not the majority, maybe 25 or 30% of the research is going toward amyloid, but there are many other targets. So inflammation is a really important target. Tau is a really important target. Aging is really important in what's called now jero science and really understanding neuronal aging and how to increase the vitality of nerve cells as we age and things that we can do to make that possible too, just in our daily life. So this is really critical. I am hopeful.

(00:31:12):
I'm a little more excited. I think about CRISPR maybe than Rudy just said. I thought that was a huge breakthrough to have the first approval. I don't think you can apply it broadly to sporadic Alzheimer's, but I think there will be a role for the genetic form, what's called autosomal dominant Alzheimer's disease to modify genes. It's a smaller segment of the population, but it could be a great proof of concept. And so I think eventually there will be treatments that are gene modifying for Alzheimer's disease. There are some, certainly in other neurodegenerative diseases, there are antisense drugs, mRNA modifying drugs. There's one being tested now for tau that looks good, has good preliminary data. We'll see how it pans out in people. It's a challenge to get the concentration high enough into brain. Right now we have to deliver this medicine into the spinal canal. So if it were to work, we'd have to think about, hopefully we could get it into an intravenous form, but right now we're delivering it through a spinal tap, so a reverse spinal tap where we put the medicine in. We'll see. But I, I'm hopeful. I just think we're on the right trajectory. And inflammation, as Rudy mentioned, that's critical. We're on the right trajectory to figure out how to combine treatments and how to obviously start earlier. That was the main focus of our first part of our discussion.

(00:32:43):
Do we have enough funding?

DR RUDY TANZI (00:32:46):
We did. I mean the last few years have been good in terms of the increased funding for Alzheimer's. But the new pay lines, that just came out a very depressing, I don't know why it went from 25% funding for Alzheimer's grants at the NIH to now. The pay line says half of that. It says 10 to 12%. I hope that when the government decides how much money goes to the NIH for Alzheimer's, that they don't think the new approved drug means the job is done because man, that couldn't be farther from the truth. So I don't know what drove this decrease. And I would love to find out because it is our governing bodies to tell the NIH how much budget they have and what goes in.

DR STEVEN SALLOWAY (00:33:32):
Well, if that's the case, we need to push back on that. I mean, it's been great, Sean, because funding was flat for years from NIH and then the Alzheimer's Association and others really advocated and worked with Congress and advocated for increased funding and then it quintupled, which has been fantastic. And the pay lines were more generous and especially for young investigators, which is great in order to attract young people into the field or people who are working in other areas of science who could bring their technique or technology to Alzheimer's research, we're also incentivized. So I'm sorry to hear that as a little backslide there because we do need that funding in order to incentivize the breakthroughs. There's no two ways about it.

DR RUDY TANZI (00:34:25):
Yeah, the NAHP lines just came out and I was shocked. We were all shocked.

DR STEVEN SALLOWAY (00:34:29):
Well, we got push back

DAVID SHENK (00:34:31):
Follow up to that without getting into the weeds of those pay lines. Let's just assume, because I'm the most optimistic guy here that that's just a mistake and lobbyists sort that out and we get back to where we were, which was a pretty impressive amount of funding.

DR STEVEN SALLOWAY (00:34:47):
Well, it's not impressive compared to heart disease or cancer. It's on par with HIV.

DAVID SHENK (00:34:52):
Okay, thank you for clarifying. That's kind of where I was going.

DR STEVEN SALLOWAY (00:34:54):

We're on par... Alzheimer's, If you think of the impact of Alzheimer's worldwide and HIV Alzheimer's in the United States Research Fund is on par with HIV currently and which is great. We were one seventh of HIV for years, and so that's good. But we're still way below heart disease and cancer and the cost of Alzheimer's care is greater than heart disease or cancer. So we're not on par with the magnitude of the problem.

DAVID SHENK (00:35:24):
And the question I want to ask is, is there more research sitting there on the shelf waiting for even more funding? That is, if it was doubled again, could you actually put that money to use tomorrow this year? Is that the choke hold?

DR RUDY TANZI (00:35:41):
Yeah, shots on goal man trials. Trials are expensive and you don't know until you try. And so we do need more smart trials that are funded and shots on goal. And so yeah, there's more research being funded and there's more trials than before being funded, but there's lots of stuff sitting on a shelf just waiting for a chance to go into a clinical trial

DAVID SHENK (00:36:06):
Just to connect the dots. If I'm a person who's in my late fifties, which I am, and I'm scared to death of Alzheimer's for my parents and now for my generation, eventually for my kids, and I'm hearing all this promising stuff and I'm hearing for the first time that we've got a theory of the case about how to stop or maybe slowed way down this disease, I've got that much more incentive to speak my mind to my elected officials and people who are controlling funding to say, Hey, we can get here faster. The scientists are waiting to spend this money. They know how to spend it intelligently. We can stop this disease sooner if we have more money to spend on. It's as simple as that. Is it that simple?

DR STEVEN SALLOWAY (00:36:56):

It's not simple, but your proposal is a good one. We should all be talking to people who make these decisions about the importance of this problem and the need for investing in research and for coverage and for access as new treatments become available. This was a big deal. I mean, we take it for granted that this first treatment lecan map, the one that is a full approval, is being covered by Medicare. That was not a done deal. That took a lot of advocacy. So anyway, the point is speaking up. We all need to speak up. So I'm glad you're covering it and I hope that your audience will speak up to their representatives. It's really important to insurance companies too.

SEAN COLLINS (00:37:47):
I have a question about journalism for a moment. I have a friend whose initials are David Shenk, who often makes the point that journalists will jump at any advance with any press release that comes from any lab and announce the end of Alzheimer's is at hand. I wonder whether there's a role in educating journalists as gatekeepers. Is there a way of educating people about how this research gets done?

DR STEVEN SALLOWAY (00:38:23):
My experience, Sean, has been the opposite. I think that there's been a skepticism among journalists, certainly with Aducanumab, which was controversial. They just went to town to kill Aducanumab. And there was something there. I mean, even though it wasn't done properly, it wasn't done optimally. There was some important information there and they tried to kill it. And I've experienced more skepticism than blind optimism. So I have an experience and I've dealt with, I've talked to a lot of reporters, and I'm sure Rudy has too. Yeah,

DR RUDY TANZI (00:38:58):
They jump on bad news and they try to make people look stupid. And they have more fun doing that because that's better clickbait than giving good news.

DR STEVEN SALLOWAY (00:39:06):

Something about, I'm telling you, there's a stigma, but that's what I'm saying, getting it out of the dungeon is there's a stigma about Alzheimer's and it's revolutionary to think that Alzheimer's is a treatable disease or preventable. That's a revolutionary concept. It is not on the journalists' radar, maybe the exception who has gotten behind this, but that has not been my experience.

DAVID SHENK (00:39:33):
Think, Sean. I think both can be true. I mean, what these guys are saying is absolutely right. And I saw the same thing, and Rudy and I have done a little writing together to try to counteract this with our friend Lisa Genova, who's just a wonderful writer on the topic, because we do need to help people understand that we've crossed this threshold and that there's some real progress. But there also is this kind of, I just see every week for the last 25 years, I'm sorry, these press releases come out and it makes some paper or some internet something somewhere, and people call me and say, oh my goodness, you see this breakthrough? And I have to explain, well, it's an exciting thing that needs to be researched, but Alzheimer's is not over. And I think it's stems from the same problem, which is, as you suggest, Sean, I think it would be incredibly useful, and you and I can talk about this off air to somehow get some really wonderful journalists in a room and find a way to really educate them about this disease and just have them talk a little bit smarter about it.

SEAN COLLINS (00:40:42):
And especially if the esteemed researchers that we have here in this conversation are both saying, we're on the verge of a whole new era. It's time to sort of reinvent the paradigm of how you tell the story of Alzheimer's.

DAVID SHENK (00:40:57):
Absolutely.

DR RUDY TANZI (00:40:59):

So taking both of these sides, right, okay, the hyped up. Good news. Maybe the journalist made too good news out of Chebe and the governing party, the US government who determines anti spreaders said, oh, we're done. And maybe that's why a pay line just got cut in half. On the other hand, people tend to want to stop and look at an accident, so they see bad news and it embarrasses somebody and says, oh, all your tax dollars would go into this hypothesis that this one person now says it is wrong. How about those stupid Alzheimer researchers wasting your money? That really hurts because journalists have so much power to influencing the government who's reading the lay papers to then make decisions on the NIH pay lines. Man. I mean, talk about needing what you just said, but will it change? Because at the end of the day, the clickbait is what makes money. So is it going to change? I dunno, I don't want to be pessimistic, but I think the press has done quite a bit of damage to this field, I have to say. I think you say, how can things go faster, not just more money, more clinical trials, but depressed behaving as well.

SEAN COLLINS (00:42:18):
Yeah.

(00:42:20):
I have yet to ask the question about what the current new treatment costs, because I think a lot of people will immediately seize on that line of argument, but is the current system of marketplace driven pharmaceutical research, is that just a given that is never going to go away? Or is there a place for public funding of drug research so that a direct government funding so that the cost of a drug might be less for people being prescribed it when it becomes available? I mean, it's one thing to say you have a new drug and another thing to say, and it's going to cost $500,000.

DR STEVEN SALLOWAY (00:43:08):
Well, this is a real challenge here because these are large molecules that were very expensive to develop. Some companies have been at this for more than 30 years with zero return and billions of invested in r and d, and these drugs are approved for cancer

and for rheumatologic diseases and et cetera, monoclonal antibodies, and they're expensive. So I think it's a real challenge to roll these out. There's so many people with Alzheimer's disease to roll these out broadly, and it turns out that only a percentage of people, these drugs are approved for people with early Alzheimer's disease. So symptomatically, they have mild cognitive impairment or mild dementia, and they have to meet certain criteria, certain safety criteria. So when you cone it down, it's going to turn out to be about 10% of all people that actually have early Alzheimer's disease. So we're not talking about treating everybody, but to treat a larger number of people, we're going to need drug, and it's just going to be too expensive. We have to find other alternatives. It's not cost effective to treat tens of millions of people with drugs that are this expensive.

DR RUDY TANZI (00:44:23):
So the new drug that can be is about $26,000 per year. But then the patients, because they risk swelling in the brain and hemorrhage, have to have a series of MRIs while they're taking it at the IV centers. So I don't know what, Steven probably knows the final figure better than me, but I've heard it can cost between 50 and a hundred thousand dollars per patient. Does that?

DR STEVEN SALLOWAY (00:44:48):
That seems a little high, but it's expensive

DR RUDY TANZI (00:44:53):
With the MRIs.

DR STEVEN SALLOWAY (00:44:54):
I get it. Well, that's a whole nother thing is actually, so we've talked about this step forward, which it is. The other important point for the audience to know is that this is a very new thing for Alzheimer's disease. We have not had an intravenous treatment that was clinically approved. And to roll this out, and with MRI monitoring and amyloid PET scans and testing for genetic risk of APOE, these are all new standards to care and

having a team to monitor it and radiologists that can detect the side effects, the most common side effects, which are swelling in the brain, that's a challenge that we're all facing. And so it's going to be difficult to roll this out, and it's not cheap.

DR RUDY TANZI (00:45:48):
So if you go from there to the fact that there could be 10 million, up to 40 million people if they had the blood test today, would find out they have amyloid in their brain and say, Hey, I want to get rid of it. Nevermind the people who just don't want amyloid to ever get there. You need small molecules, little white pills that do the same thing for a fraction of the cost and with a much better safety profile. And to answer your question about public, I mean odd drug that we developed, the gamma secretase modulator, which we feel has maybe the best chance in the world to become the statin of Alzheimer's, was funded by the NIH and Cure Alzheimer's Fund. The NIH has something called a Neurotherapeutics blueprint where they will fund development of your drugs and give you pharmaceutical company like advice. So they have X pharma people advising you.

(00:46:39):
And so all told over the last 20 years between foundations like Cure Alzheimer's Fund and the NIH, I think about over 30 million went. It's a development of our drug, and now it's finally at the FDA waiting for a chance to go into a safety trial next year. And for that, it's going to cost more money now. But the NIH even agreed to pay for the safety trial. So you know what they're doing their job, we just need more money for them to do more jobs. And if this drug works, it will be one contender, maybe the main contender to be a safer, more affordable alternative that can be democratized across the population. But I

DR STEVEN SALLOWAY (00:47:25):
Think there could be more. To answer your question, Sean, there are more models of public-private partnership, which Rudy's referring to that, for example, with Kinumab, there is a prevention trial for people who are cognitively normal but are building up

plaques or just beginning to build up plaques, testing this amyloid lowering drug. And that's a combination between the manufacturer, ACI and Biogen, their partner and the NI National Institute of Aging through an Alzheimer's consortium. So there are more models of that and there should be even more. But fundamentally still, the pharma companies have the lead in drug development. The most of the investment comes from the pharma side.

SEAN COLLINS (00:48:15):
Maybe that point naturally leads to this question. I hope it does. What is the role of imagination at this stage of the disease process for people like yourself who are looking at these advances and working on these advances? How much of the next advance or the future is going to come from one or both of you or one of your colleagues sitting in front of a fireplace with a cup of tea, imagining what a future could look like or imagining a therapy that might work? What is the role for imagination for you guys?

DR RUDY TANZI (00:49:01):
I think imagination has to be driven, has to be seeded. And so a lot of the studies that I like the best that we do, we say are agnostic, meaning you're screening for new Alzheimer's genes using new algorithms, which is my bread and butter in my lab is scanning the genome for new genes. And then when you get the new genes, most of the time you say, what the heck is that? You got to look it up. Then you have to use your imagination to say, okay, so this gene, all the statistics say without a doubt, this is an Alzheimer's gene. Just like when we first found that CD 33 gene and didn't know what it did. And then you got to use your imagination and say, how might this gene cause the disease and how might that suggest new therapies? The second agnostic set of experiments, that CD imagination is when you without bias screen all of the approved drugs like we just did, we invented Alzheimer's in a dish.

(00:50:01):

The first mini human brain organoid the size of a pea that made drug screening, unbiased drug screening of all the approved known drugs in the world, a hundred times cheaper and 10 times faster than when we have to do one at a time in the past in mice. So then we get these drugs out and you're like, whoa, what the heck are these drugs? Right? I got to go to Steven and say, what's this drug do? What's this drug do? And then you have to use your imagination and say, what are these drugs that are working? These drugs that stopping tangles to stop the amyloid, these drugs that are making the microglial cells eat the amyloid and get rid of it? The radio Kem does. And now you have to use your imagination and say, what do they have in common and what are they teaching us about the disease? And actually that's been the most fun I've had in the last five or 10 years in research, is the imagination driven by unbiased data that comes out of agnostic screens. I mean, that's like a researcher's dream, but if you just go in there with only imagination, without something to see that, yeah, you might take a lot of warm guesses.

DR STEVEN SALLOWAY (00:51:05):
Well, I think Rudy just really hit it. If you take a team that has a solid foundation in science that has a spirit of discovery and then has imagination to take their findings and try to see where can they lead and test them in an open kind of way, then get enough talented people, you're going to come up with some great stuff and stuff. There are things I think that Rudy and I have imagined, but there are things that we have not yet imagined that will be become the standard of care either in our lifetime or before too long.

DR RUDY TANZI (00:51:43):
You got to think out of the box, but you have to still be a distance away where you can see the box.

SEAN COLLINS (00:51:50):
David Shenk, I'm going to give you the last word.

DAVID SHENK (00:51:53):
Well, I'm going to step a few steps away from the box to say that there's a new book called The Day After Yesterday, which is a book of beautiful photographs and biographies of people who suffer from Alzheimer's disease by a wonderful photographer named Joe Wallace. Rudy knows him. He contributed to the book, and I was able to help a little bit too. And I think we've made a lot of progress in helping the world get to know people with Alzheimer's disease and really getting to know, really empathizing with this enormous problem that by now almost everyone in the world is touched with in some way. What we haven't done a very good job, a good enough job as journalists, Sean, you and I, representing the media out there for the moment, is to help the world get to know the absolutely brilliant and giant hearted scientists represented here by Rudy and Steve.

(00:52:55):
I happen to know, I knew Steve Wagner, who worked closely with Rudy on that drug that he's been talking about. Never was there a sweeter, more generous, brilliant, warm person. And there are so many others that these guys know women and men who are out there, a giant army of people who have quietly brought us to this new very, very hopeful place. And I wish there were a way for brilliant people in the media to get to know the brilliant people in the science world better and that they could trust each other more. And maybe good ideas would come out of that. But one thing that I know would come out of that is more better communication about what we know now, what ideas we can trust, how we can impart those ideas to the general public, and then how we can use those ideas to get to a cure faster.

SEAN COLLINS (00:53:55):
David Shenk, Rudy Tanzi. Steven Salloway, thank you for the conversation. I'm really grateful. Good luck in 2024 and happy New Year.

DAVID SHENK (00:54:05):
Let's talk again.

(00:54:06):
Thank you. Happy holidays.

DR STEVEN SALLOWAY (00:54:07):
Happy holidays. Thanks for having us.

SEAN COLLINS (00:54:10):
Dr. Steven Salloway is founding director of the Memory and Aging Program at Butler Hospital in Providence, Rhode Island, and a professor of psychiatry and human behavior and professor of neurology at the Warren Alpert Medical School at Brown University.

(00:54:27):
Dr. Rudy Tanzi directs the Genetics and Aging Research Unit at Massachusetts General Hospital. Director of the McCance Center for Brain Health at Mass General, Dr. Tanzi is professor of neurology at Harvard Medical School.

(00:54:43):
And David Shenk is a national bestselling author of six books, including "The Forgetting — Alzheimer's: Portrait of An Epidemic."

(00:54:52):
Late in the year 1901, right at the cusp between autumn and winter, a woman was admitted to the hospital for the mentally ill and epileptics in Frankfurt. She was seen by one of the hospital's senior physicians, Dr. Alois Alzheimer. She had a remarkable cluster of symptoms, especially remarkable because of the woman's relatively young age. She was 51 years old,

DR ALOIS ALZHEIMER (actor) (00:55:28):

Reduced comprehension on memory, aphasia, disorientation, unpredictable behavior, paranoia, auditory hallucinations, and pronounced psychosocial impairment

SEAN COLLINS (00:55:49):
For the next five years, and in three hospitals — in Frankfurt, in Heidelberg, and finally in Munich, Dr. Alzheimer would document the illness of his patient keeping a record in a blue cardboard file folder in both Latin script and in that now-outdated German style of handwriting. The case history begins the morning after her admission to the hospital,

DR ALOIS ALZHEIMER (actor) (00:56:15):
26 November, 1901 She sits on the bed with a helpless expression. What is your name? Auguste, last name, Auguste. What is your husband's name? Auguste? I think. At lunch she eats cauliflower and pork. Asked what she's eating, she answers spinach

SEAN COLLINS (00:56:56):
In the days that would follow Alois Alzheimer would continue to document the illness of his patient,

DR ALOIS ALZHEIMER (actor) (00:57:01):
Asked to write Auguste D. She tries to write Mrs and forgets the rest. It is necessary to repeat every word. Amnestic writing disorder. In the evening, her spontaneous speech is full of phasic, derailments and perseverations. The patient is asked to recognize objects by touch with her eyes closed, a toothbrush, sponge bread, spoon, brush, glass knife, fork plate, purse mark, cigar key. She recognizes them quickly and correctly. By touch, She calls a brass cup, a milk jug, a teaspoon. But when she opens her eyes, she immediately says a cup. When she has to write Mrs. Auguste D, she writes, Mrs. And we must repeat the other words because she forgets them. The patient is not able to progress in writing and repeats. "I have lost myself. I have lost myself."

SEAN COLLINS (00:58:46):

Auguste Deter died in April of 1906. The cause of her death was septicemia -- blood poisoning that resulted from bedsores. Dr. Alzheimer asked to be given custody of her medical record and of her brain, which he studied. He'd go on to describe for the very first time the tangles and plaques that are the anatomical hallmarks of the disease that bears his name today. His drawings of those details of Auguste Deter's brain, the woman who told him she had lost herself, are hauntingly prescient. The precise significance of those plaques and tangles could not have been understood in 1906 and yet Alzheimer's detailed drawings of what he saw under the microscope tell us he somehow grasped their importance in that pathology lab in Munich at the beginning of the last century.

(00:59:51):
Today, even as we come to a greater and greater understanding of the significance of those plaques and tangles, we can say that the days of people losing themselves to Alzheimer's disease, to families loving someone who appears to have forgotten their life, the end of those days, the end of Alzheimer's, may be very near.

(01:00:27):
The Hear Me Now Podcast is a production of the Providence Health System and its family of organizations. We invite you to subscribe at hearmeowpodcast.org

(01:00:38):
The program is produced by Scott Acord and Melody Fawcett. We have research help from medical library staff Basia Delawska-Elliot, Sarah Viscusso, Carrie Grinstead, and Heather Martin. The entries from Alois Alzheimer's clinical notes were read by Thomas Barclay.

(01:00:59):
Our theme music was written by Roger Neill. The executive producer is Michael Drummond.

(01:01:04):
Join us in two weeks when we'll be looking ahead in 2024 and asking a panel of clinicians about what they're expecting in their fields in the year ahead. It's a way for us to focus our attention at the beginning of the year on the increasingly complex world that makes up medicine in the 21st century.

(01:01:27):
I'm Sean Collins. Thanks for listening this year. Be well.