

Harvard Medical Labcast

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The A-Word

Trying to catch Alzheimer's disease before symptoms appear

Reisa Sperling

Interviewers: Stephanie Dutchen, David Cameron

STEPHANIE DUTCHEM: Hello.

DAVID CAMERON: Hello.

DUTCHEM: Hello!

Hello, and welcome to the October 2015 Harvard Medical Labcast. This podcast is brought to you by Harvard Medical School's Office of Communications in Boston. I'm Stephanie Dutchen.

CAMERON: And I'm David Cameron.

DUTCHEM: In this episode, David tells us about PERVs.

CAMERON: Yes. And we will talk about the actual technical name for this class of molecules, for which PERVs is the unfortunate acronym.

DUTCHEM: You mean, the awesome acronym.

CAMERON: For which PERVs is the awesomely unfortunate acronym. And in our conversation, Stephanie speaks with Alzheimer's expert Reisa Sperling. Stephanie, do you want to tell us a little bit about that conversation?

DUTCHEM: Sure. Reisa is a professor of neurology at Brigham and Women's Hospital. And we had a great talk about her personal family connection with Alzheimer's disease.

How that got her interested in studying it. And some of the work that she's been doing, both with patients individually and with clinical research.

CAMERON: Great. Well, we'll listen to that. And then we'll get to PERVs.

DUTCHEM: Sounds good.

[MUSIC PLAYS]

DUTCHEM: We are here this morning with Dr. Reisa Sperling, an Alzheimer's disease researcher. Thank you very much for coming in to talk with us.

REISA SPERLING: Thank you so much for having me.

DUTCHEM: So I understand you have a personal connection to the disease that you study. Would you share a little bit about how you became interested in studying this disease?

SPERLING: Certainly. So at the time I was thinking about whether to go to medical school, unfortunately, my grandfather, with whom I was very close, started to act strangely. And at the time, people called this hardening of the arteries; they didn't really understand the "A-word" or Alzheimer's disease yet.

And I realized later that he was developing Alzheimer's disease and sadly he died when I was a neurology resident.

DUTCHEM: Sorry.

SPERLING: Well, it's been a personal motivation. And unfortunately, my father was also diagnosed last year. So I have to say that every day, between my own family and the patients I see, I'm very motivated.

But also there's an incredible scientific curiosity about Alzheimer's disease. You know, memory, we don't really understand where it lives in the brain. How it works. It's such an integral part of each of us. And sadly, Alzheimer's disease is a perfect example of how it disappears.

DUTCHEN: Yeah, I mean, take your story and multiply it five million times across the U.S. right now, or more, for multiple family members. And it's heartbreaking.

SPERLING: Absolutely. There's really very few people who aren't affected by Alzheimer's disease in some way. And it's not something we think about on a daily basis. And yet, it has a huge impact on families and disproportionately I think on women because we're often in the sandwich generation. We just get done taking care of our kids and then end up taking care of our parents. So I hope we'll make this more of a public health conversation.

You know, when I was in medical school, people were afraid to say the "C-word." And when people started talking about cancer and wearing ribbons and making this a public national conversation, things really changed. And I feel like we're just on the precipice of being able to do this for Alzheimer's disease. And I think once we start talking about it and realize how much it impacts every family, we'll really make a difference.

DUTCHEN: I would say that sounds nice, but I'm not sure that's the word for it. But it sounds like progress.

SPERLING: Yes. So it's not a nice word. But I think we someday should make it a word that we think about as a preventable illness. And this is the way we get there.

DUTCHEN: So your work focuses on the early detection of Alzheimer's, because right now by the time people are diagnosed, there's extensive damage in their brains.

SPERLING: Absolutely. So we still think of Alzheimer's disease as being diagnosed at the stage of what we call dementia. And this is a progressive cognitive decline. But at that point, people unfortunately have lost many of the nerve cells in their brain. And it's unlikely at this point we can grow them back.

So I think our best chance is to detect Alzheimer's disease ideally before there are any symptoms at all, just like we do in cancer and heart disease and diabetes -- we do lab tests and imaging tests to be able to detect disease before it gets to the stage of irreversible damage. And I think we can do that in Alzheimer's disease quite well right now.

DUTCHEN: Well, that's great. So how do we get to that stage where we can help people before they develop these irreversible symptoms?

SPERLING: Well, we know that one of the major brain changes in Alzheimer's disease [is] the accumulation of something we call amyloid. It accumulates in plaques that we can now see with PET scans and with other tests probably 10 or 20 years before we get to the stage of dementia.

Sometimes I think of it like cholesterol. We have a test or we can look in a blood test for cholesterol going up. And we learned a lot about cholesterol in different forms and how that can predict a heart attack or a stroke. I think we have the ability in Alzheimer's disease to detect amyloid very early.

DUTCHEN: So instead of building up in the arteries, it's building up in the brain.

SPERLING: Absolutely. We don't yet have a blood test in the same way we do for cholesterol. But we do have imaging tests, especially something we call PET scans that are very sensitive and are able to pick up even relatively small amounts of amyloid plaque in the brain. And we see that about 30 percent of people over the age of 65 already have some amyloid plaque buildup in their brain. And about 30 percent of seniors will die with dementia.

It's estimated it's probably about 15 to 20 years between the plaque buildup and the stages of dementia that are probably irreversible. So for me, that's a glass half full. You've got 15 years to get in there, hopefully treat people, and prevent them from getting to the horrible stage of Alzheimer's disease.

DUTCHEN: Now, if I'm not mistaken, there is a fierce debate in the field as to whether amyloid-beta is actually causing these symptoms or whether it's this other protein called tau. So how do we figure that out?

SPERLING: Well, you're absolutely right. Our field has been fighting for 30 years about whether it's amyloid or tau. Sometimes we call it the amyloid beta, or the Baptists, versus the "Tauists." But really I think this is a silly debate at this point. It's clear that it's both. And that the more we look, the more we see evidence that amyloid and tau are related even before people get symptoms.

When we can see evidence on PET scans now of amyloid buildup, we see about half of those individuals also have tau buildup. And therefore, I think if we could interfere with amyloid early enough, we might be able to prevent tau. And I think we should go after both. Ultimately, we'll have combination therapy.

DUTCHEN: Now, if I remember correctly some of the work that you've done both on the basic science side and the clinical science side have started to untangle, which is a terrible pun, some of what's going on so that you can take another step forward toward trying to be able to develop biomarkers and treatments. Can we talk more about the discoveries that you've made?

SPERLING: Absolutely. So I think one of the first discoveries is really that the amyloid protein builds up 20 years before dementia. And very soon, if not simultaneously, the tau builds up and tangles. So it's not really a bad pun. We've been working hard to disentangle the relationship between amyloid and tau.

And most importantly, because we do have promising experimental treatments, at least for the amyloid part of the story right now. And our hope is that if we can interfere with the amyloid early enough, we'll prevent the tangles from spreading. And that's the idea behind the A4 study.

DUTCHEN: What is the A4 study?

SPERLING: So A4 stands for "anti-amyloid in asymptomatic Alzheimer's disease." So you can imagine why we had to call it A4.

DUTCHEN: Yeah, less of a mouthful.

SPERLING: Exactly. So this is a first-of-its-kind trial of what we call a secondary prevention trial. That is, people who have evidence of early Alzheimer's disease in their brain, but don't yet have symptoms. And this is a very large, over 1,000-person trial in the U.S., Canada and Australia. And it's what we call a phase three trial, which means if this is positive, this drug would have a potential to get to many people in the world to be able to prevent Alzheimer's disease.

DUTCHEN: So is part of the trial then to figure out who develops Alzheimer's and who doesn't and what their brains look like?

SPERLING: Absolutely. So the A4 study has several components. The first component is that we really have three arms. So we have an arm of individuals who have evidence of amyloid plaque buildup in their brains. And they will get treated with an antibody against amyloid.

The second arm is what we call a placebo arm. These are individuals who also have amyloid plaque buildup in their brain, but for the first three years of the study they'll get placebo or a saltwater infusion instead of the antibody.

And then the third arm, which is called the LEARN study. And that stands for Longitudinal Evaluation of Amyloid Risk and Neurodegeneration. And this is really looking at what are the other things that change in the brain when there is not elevated amyloid. And that study's funded by the Alzheimer's Association.

And we hope by the end of the study that not only will we be able to see that a treatment if given at the right time can slow decline, but we also can better quantify what is the decline related to the amyloid plaques. And what are the other contributing factors that relate to memory loss in older individuals. Because someday we'll treat with combinations of therapies going after many different mechanisms.

DUTCHEN: Right. Now, I also seem to remember that there are some people who develop amyloid plaques, but don't develop the symptoms of Alzheimer's. So would this study uncover maybe what's going on there as well?

SPERLING: Absolutely. So we know that there are some people who have evidence of amyloid plaque buildup in their brains, but seem to be relatively resilient to the amyloid plaque buildup. And we have some clues already that there may be genetic factors that influence that. Some of the risk genes for Alzheimer's disease, such as one called apolipoprotein E4, or APOE4, not only does it increase amyloid, but in the setting of having amyloid, it may make people, unfortunately, more vulnerable to decline. And there are likely protective genes that we haven't even discovered yet.

We do have evidence, though, that most people who have a lot of amyloid plaque buildup will decline over time. But some will never get to the stage of Alzheimer's dementia in their lifetime. And that's terrific.

We treat people with cholesterol-lowering agents. And less than 2 percent of people with high cholesterol will ever have a heart attack or a stroke. But by decreasing it at a

population level, we've decreased the morbidity or the problems associated with heart disease by 28 percent.

So I think in Alzheimer's disease it may be the case that treating amyloid early, we will treat some people who will die of something else before they get dementia. But I hope it will mean that we will allow people to die ballroom-dancing healthy instead of in nursing homes.

DUTCHEN: That's perhaps what some would call a sunny outlook.

SPERLING: Well, I have been accused of being a Pollyanna. But I really do feel like now is a special time in Alzheimer's disease. The ability to detect disease before symptoms is really the way we've made progress in almost every other disease where there have really been medical breakthroughs. Particularly, in HIV/AIDS, cancer, diabetes, osteoporosis. So I'm really hopeful that this will allow us to make real progress in Alzheimer's disease.

And I think it's also an important time from a public health impact. People are realizing, unfortunately, that if one out of every nine individuals over the age of 65 has Alzheimer's disease, that we've got to do something about this urgently as our population is growing older very fast.

DUTCHEN: Yes. Now, you are also involved in other clinical trials for Alzheimer's. Is that right?

SPERLING: Absolutely. So although my focus is really on prevention of dementia and symptoms, I do think it's critically important to offer trials for people who already have symptoms. And so we run trials in people who have very mild symptoms, at what we call mild cognitive impairment stage, and also people who have mild Alzheimer's dementia. And although I think these treatments will work best 10 years earlier, it's critically important to do studies in people who are already suffering from this disease as well.

DUTCHEM: So you've been working on these clinical trials for not a super long time now. I think they're still recruiting. Right?

SPERLING: Absolutely. The A4 study is open right now for people age 65 to 85.

DUTCHEM: That's our advertising pitch! But you say that there is already science that's coming out of it. Things that you're learning.

SPERLING: Absolutely. So in what we call the screening process for the A4 study, we'll be getting about 3,000 PET scans on clinically normal older individuals. And that is already teaching us what the factors are that increase the likelihood that someone does have evidence of amyloid plaque buildup.

And an important thing about the A4 study is, because it's a public-private partnership, all of those results and actually the raw data are going to be made available to the field, as well as blood samples, so that other scientists can look for evidence of blood tests that we could do.

DUTCHEM: That's great. Because it sounds like you really need a solid foundation of what's going on in everybody's brains before you can start building on that to figure out biomarkers, interventions, treatments.

SPERLING: Absolutely. So although I think the A4 study, the first of its kind, will be critically important, I suspect it's only the first of many studies. And we hope that the screening data from the A4 study being made available to the field will make the next study -- A5, A6, A7 -- even more efficient and help us get there faster.

DUTCHEM: And you see patients as well in your clinical practice?

SPERLING: I do. I am a clinical neurologist. And although I spend 99 percent of my time in clinical research, I really do like seeing patients. Unfortunately, there is nothing quite as motivating as seeing someone decline over time into the depths of despair of Alzheimer's disease. And feeling like I don't have anything right now that can really slow that process or what we call disease-modifying therapy. So it's important to both give people hope and learn about this disease, but ultimately really work to prevent it.

DUTCHEN: Well, I hope that in another five, ten, fifteen years we can check in with you and we'll have made immense progress in this area.

SPERLING: I certainly hope it's closer to five than fifteen years, but I'd be happy to update you.

DUTCHEN: Thank you so much for coming to talk to us today.

SPERLING: Thank you, again, for having me.

[MUSIC PLAYS]

TELEVISION CLIP: I just saw a pig man. A pig man! You know, he was sleeping. And then he woke up and he looked at me. And he made this horrible sound. This [SQUEALING].

CAMERON: Ah, that voice. That's Kramer from the sitcom "Seinfeld," convinced that scientists are genetically engineering an army of human-pig hybrids. Now, before you get your hopes up, this is not going to be a report on Harvard Medical School scientists engineering an army of human-pig hybrids. Sorry.

However, in a new study that I'm sure Kramer would be totally cool with, researchers report using the new gene-editing system CRISPR to simultaneously edit 62 discrete locations in the pig genome in order to make pig organs safe to use one day in people.

Now, first, this represents an explosive leap in CRISPR's capabilities. Prior to this, the system was only able to simultaneously edit six regions of the genome. But even more to the point, the 62 locations targeted by CRISPR end up disabling a class of retroviruses native to pigs called porcine endogenous retrovirus, otherwise known as, as we mentioned earlier, PERVs.

This class of molecules has so far inhibited researchers from considering transplanting pig organs into human patients. And this is important. Currently, there are more than 120,000 patients in the U.S. awaiting transplants. But fewer than 30,000 transplants are performed each year. That leaves 90,000 patients waiting.

Transplanting organs from certain animals -- something that's known as xenotransplantation -- could give patients and clinicians a life-saving alternative in the future. And this new study helps provide a way.

[MUSIC PLAYS]

DUTCHEN: David, we're going to try the ending your way this time--

CAMERON: OK.

DUTCHEN: --with a terrible science joke.

CAMERON: Awesome.

DUTCHEN: This time brought to us by Jon Clardy in HMS's Department of Biological Chemistry and Molecular Pharmacology.

JON CLARDY: A chemist, a physicist and a mathematician were taking a train into Scotland.

DUTCHEN: OK.

CLARDY: The chemist looks out the window, sees a black sheep, and says, “Hey, the sheep in Scotland are black.” And the physicist says, “At least one sheep in Scotland is black.” And the mathematician says, “At least one side of one sheep in Scotland is black.”

DUTCHEN: ...Ba dum shh.

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