

The Boston Globe

# Cracking an intriguing secret of centenarians: Why so few are ravaged by Alzheimer's disease

By *Kay Lazar* Globe Staff, May 6, 2023

When Herlda Senhouse looks back — way back — in time, she vividly remembers the smells — the sour tang of the beer she siphoned into bottles on her first job while still in grammar school in the early 1920s and the pervasive rotten egg odor from the paper mill near her childhood home in West Virginia.

Sitting at the dining room table in her Wellesley apartment, Senhouse, a slight woman with a smooth-as-honey Southern accent, is quick to summon memories and to offer tips — the best local restaurants for strawberry shortcake, or her favorite, sautéed calves liver.

And, without hesitating, Senhouse names Franklin Delano Roosevelt, who served during the Depression, as tied with Barack Obama for her favorite among the 19 presidents she's witnessed in her 112 years.

"He did such wonderful things for the people," she said, speaking of FDR.

Senhouse is the rarest of rarities. Only about one in 5,000 people in the United States is a centenarian. (About 1,900 centenarians live in Massachusetts, according to 2021 federal records.) And the odds of reaching 110 are rarer still: just one in 5 million.



112-year-old Herlda Senhouse sat at her dining room table at her home in Wellesley. JESSICA RINALDI/GLOBE STAFF



A photo of Herlda Senhouse, (center, wearing white) from her graduating class at Woburn High School in 1931. JESSICA RINALDI/GLOBE STAFF

But it's not just longevity that makes Senhouse exceptional. Her clear memory and sharp thinking are hallmarks of super agers, as these ancients are known; so is her generally good health. Major age-related illnesses hit most centenarians about 20 to 30 years later than everyone else. And few ever develop Alzheimer's disease.

Increasingly, scientists believe that genes, and not necessarily good habits, determine who lives past 100. Many people who exercise regularly, eat healthy diets, and refrain from smoking will make it to 90. Beyond that is when researchers say genetics plays a much larger role.

But which genes, among the thousands in a person's body, might confer longevity?

A group of Boston researchers is blazing an unusual path in a quest for answers. They aren't, like so many of their peers, looking for genes that cause disease as people age, but rather ones that protect against the ravages of aging.

“We can learn why these people delay or escape Alzheimer’s disease, and use that to come up with drugs to combat it much earlier in a person’s life, so they don’t get the disease,” said Dr. Thomas Perls, a professor at Boston University Chobanian & Avedisian School of Medicine and lead researcher of a new study on centenarians and Alzheimer’s.

Senhouse attributes her clear mind to a social schedule that would keep someone else half her age hopping: dinners and luncheons out with friends, a visit to Encore casino — she plays only the penny slots and with a strict \$20 limit — going to movies and traveling. She has crisscrossed the world over her decades, from South Africa and Hawaii to the Bahamas and Jamaica, as well as Greece and Turkey.

It’s her worldwide adventures that she most treasures.

“Traveling, and seeing different countries and different cultures and meeting different people,” are what stands out, she said.

## House calls

Perls, a geriatrician who relishes his many road trips to visit centenarians, was beaming when he walked through the door to Senhouse’s apartment on a recent visit.

“I just want to say how thankful I am to be here again to see you,” Perls said, as he hugged Senhouse and they chatted about meeting more than eight years ago, when Senhouse was enrolled in another Perls study.

“I guess it has been that long,” Senhouse mused. “You know, time flies.”

Perls has been studying centenarians for three decades.

His latest study involves collaborating with Boston Medical Center and Massachusetts General Hospital scientists to create a “brain in a dish” — a tiny, simplified version of a brain, spun from the blood cells of centenarians — and then to scrutinize how the cells behave when they encounter amyloid, the sticky protein that builds up in the brains of people with Alzheimer’s.



Dr. Thomas Perls, a Boston University researcher who has the largest study of centenarians and their families in the world, sat with Herlda Senhouse.  
JESSICA RINALDI/GLOBE STAFF

Perls and his colleagues aim to pinpoint the genetic variants that appear to protect centenarians from the devastation of Alzheimer's, the most common cause of dementia, and then design drugs that may harness that power or identify existing drugs that mimic its effect.

With more than 6 million Americans estimated to be living with Alzheimer's — a number that is expected to grow with the aging of the baby boom generation — and new drugs showing only modest success, the urgency to find effective treatments is palpable.

The Perls team is enrolling roughly 1,000 centenarians and their children in the study because he believes longevity is buried in people's genes and passed down through generations. Each will undergo memory and other cognitive testing, brain imaging, and blood sampling.

They also anticipate 100 of the centenarians will agree to bequeath their brains for study. Because centenarians are so rare, there's not a large collection of their brains anywhere for researchers to examine.



Dr. Stacy Andersen is co-researcher in the Alzheimer's study and codirector of the New England Centenarian Study. JESSICA RINALDI/GLOBE STAFF

"We'll be able to study how their brain has held up over 100 years, [using] actual brain tissue," said Stacy Andersen, co-researcher in the Alzheimer's study and codirector of the New England Centenarian Study, the databank of centenarians and their families started by Perls in 1995.

"This will allow us to see if there are proteins [in the brain] that we don't know about yet, and whether they cause or protect against neurodegenerative diseases."

The researchers have already found that children of centenarians have markedly reduced rates of heart attack, stroke, cancer, diabetes, and hypertension compared to people born around the same time who do not have a centenarian parent. These offspring also age better cognitively compared to older adults without a family history of extreme longevity.

The Alzheimer's study is also enrolling spouses of the centenarians' children as a comparison or control group.

"They share the same environment, they probably share a lot of the same health behaviors and leisure activities as the centenarians' offspring, but they don't have at least some of the protective genes," Andersen said.

"So the [tests and blood samples from] spouses can help us get at what are the genetic contributors to healthy brain aging, versus what are the behavioral and health factors that contribute," she said.

On Andersen's office wall is a framed photo that reminds her of what is possible: a picture of her in Rome visiting her great aunt Cecilia, who died in 2017 at the age of 115.

## The way-back machine

Blood samples from Senhouse and others in the centenarians' study are sent to the Center for Regenerative Medicine, a third-of-an-acre research behemoth on the Boston University Medical Campus.



Amid rows and rows of scientists' benches, and rooms stocked from floor to ceiling with tubes, bottles, freezers, and state-of-the-art machines, researchers manipulate cells to study and design therapies for some of the most vexing diseases, from Alzheimer's to sickle cell anemia.

Here, BU associate professor George Murphy, a cofounder of the center and a key member of the Perls team, reprograms blood samples through a sort of way-back machine to become pluripotent stem cells. He's essentially transforming them to an early stage of cell development where they can then be coaxed into any type of human tissue or cell, such as a neuron, to study and treat brain disorders.

"In essence, it's like the subject or the patient in a dish," Murphy said. "For all intents and purposes, that's the person, and we don't need to get another sample from them because we can make an infinite supply of cells to then look at all the things that might play into their ability to potentially escape age-related disease."

That first step, from sample transformed to stem cell, takes about 30 days, "if all goes well," Murphy said.

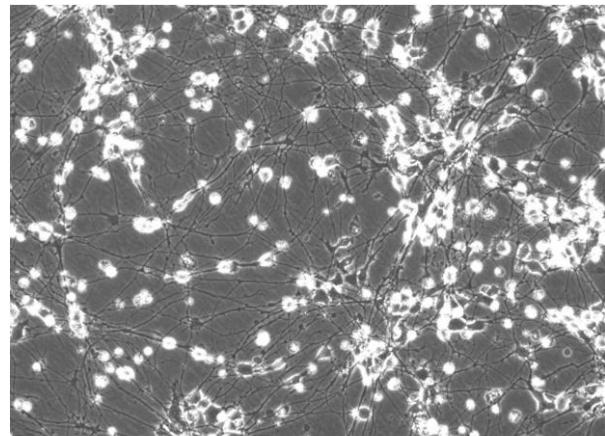
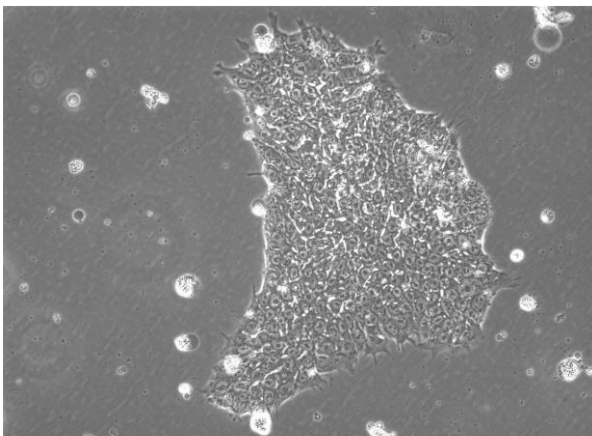
Looking through a microscope, one centenarian's sample spun into a stem cell looks like dense islands made up of tiny dots. It takes another month or two for Murphy and his team to coax the stem cells into becoming neurons by using growth factors and other substances that mimic in a lab dish what happens in the human body.

The neurons grow tiny extensions that lay the foundation for the cells to be able to communicate with one another, and the scientists use machines to detect their electrical signals, which is how the cells in the brain process and transmit information.

Murphy's team plans to compare the neurons from centenarians to neurons from two other groups: younger people who have no history of longevity in their family, as well as those who have developed Alzheimer's or other forms of neurodegeneration.



Dr. George Murphy, codirector of the Center for Regenerative Medicine at the BU School of Medicine.  
LANE TURNER/GLOBE STAFF



The microscopic view of a blood sample taken from one of the centenarians after it is reprogrammed to become a pluripotent stem cell. Four days after a pluripotent stem cell is reprogrammed to become a neuron, it is already developing extensions, a hallmark of a neuron. TODD DOWREY

They'll test what happens when they "stress" each sample, mimicking in a dish one source of aging and disease in humans by adding small molecules that disrupt a protein-regulating process that maintains cell health and function. They'll also record whether and how each dish of brain cells reacts, perhaps dying off or shortening their extensions in response to the "stress."

"We can't access the brain tissue of a [living] centenarian," Murphy said. "But in this case, we can make as much as we want from these particular people to run however number of assays and cell types. And basically, it's just a beautiful thing."

## Next stop: Alzheimer's brain in a dish

Nine years ago, Harvard Medical School researchers Doo Yeon Kim and Rudolph Tanzi pioneered a tiny, three-dimensional model of a brain in a lab dish — picture drops of egg yolk in clear gel. The model is made of cells that are engineered to produce sticky amyloid plaques and tau tangles, the hallmarks of Alzheimer's disease.

Hailed as a revolutionary method to both track Alzheimer's at the cellular level, and to quickly test potential treatments, the model can be grown in warp speed — about six weeks — compared to nearly a year for amyloid plaques to grow in the brain of a lab mouse. It's also cheaper.

For the centenarians' study, the duo will be taking stem cells created by Murphy to build their brain-in-a-dish with three distinct types of cells: the neurons created from centenarians' blood samples; microglial cells, which are like "trash collectors" that help clear cellular debris that accumulates in the brain; and astrocytes, which support neurons but also clear debris.

In Alzheimer's, the microglial cells and astrocytes go haywire and stop clearing the trash. They also release chemicals that cause inflammation, damaging the neurons they're supposed to protect.

The team's theory is that centenarians may develop Alzheimer's plaques and tangles but something in their genes protects them from the resulting cascade of inflammation that is so devastating to brain cells.



100-year-old Millie Flashman still takes ethics courses online.  
JESSICA RINALDI/GLOBE STAFF

In other words, centenarians like Millie Flashman, a 100-year-old retired professor of social work in Newton who still takes ethics courses online, may have genes that have long protected her and several of her long-lived siblings, including a brother who died from a stomach virus at age 96.

Flashman recently enrolled in the New England Centenarian Study, and the researchers will be choosing candidates from two other ongoing studies within that pool for the Alzheimer's study. Flashman's uncle, Joe Goldstein, an outgoing man who died at 102, was among the first batch of centenarians Perls enrolled decades ago.

"I gave up driving just before COVID," Flashman said. "But going to classes, taking courses, it keeps me going."

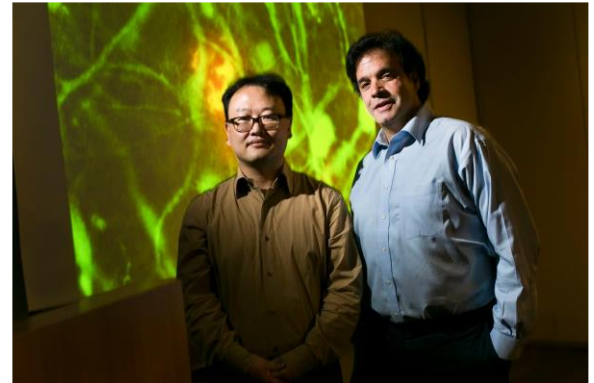
Kim and Tanzi will first compare genes within the cells of centenarians, like Flashman, to a control group to hunt for potential variations.

“We want to see what is different in the centenarian group,” Kim said. “And among those differences, what makes them resilient against Alzheimer’s.”

As Tanzi puts it: “Is it that their microglial cells stay chilled out? Or . . . do the neurons somehow have a bulletproof vest against the ravages of inflammation?”

As they lay out their theories of what’s driving the remarkable resilience of centenarians, the two scientists often finish each other’s sentences, Tanzi interjecting a sweeping vision of what is possible and Kim offering the laser-like focus to make it happen.

They hope to identify gene mutations in centenarians that convey protection against the Alzheimer’s onslaught. They would then put those genes into the cells from a control group to test, in their Alzheimer’s-in-a-dish model, whether the cells, beefed up with centenarian genes, are similarly resilient against amyloid plaques.



Neurologists Doo Yeon Kim (left) and Rudolph Tanzi in front of a colored slide of neurons in green and plaque in orange, at Massachusetts General Hospital in 2014. NYT

And if they verify that those are the target genes, they’ll be able to quickly test new drugs using their model or test medications that are already approved for other diseases but may be able to be repurposed to treat Alzheimer’s.

The idea, said Tanzi, is to “pharmaceutically mimic that resilience, so everyone can enjoy the benefits that centenarians have naturally.”

## The road ahead

It’s an open question how long it will be before the Perls team pinpoints and verifies the centenarian genes they believe provide protection against Alzheimer’s. The National Institute on Aging has committed roughly \$20 million toward the study.

“Our research is funded by the taxpayers, and they are going to want to see discoveries as quickly as possible,” Perls said.

The funding comes with a requirement that the researchers promptly share their data with other scientists.

“Personally I am very happy to do that,” Perls said. “I have long felt that the centenarians will be a very valuable resource for how people age slowly and escape these diseases and I would love to see these resources developed while I am still living.”

Dr. Nir Barzilai, scientific director for the American Federation for Aging Research, has also long studied centenarians. Though his approach to studying Alzheimer’s in centenarians is different from Perls’s, he agrees their genes may hold critical clues to treating age-related diseases.

The two have collaborated on other studies, but Barzilai is not involved in this one. He is, however, lead researcher on a national study known as the TAME Trial — Targeting Aging with Metformin — which will study metformin, a drug used to treat type 2 diabetes, to see whether people taking it experience delayed development or progression of age-related chronic diseases, such as heart disease, cancer, and dementia.

“If we are going to be healthier longer, it will be a huge boost for the economy,” Barzilai said. “It’s not about elongating life, it’s about elevating health.”

Herlda Senhouse, the 112-year-old in Wellesley, says her health is still pretty good, but she notices her eyesight and hearing are beginning to fade; she needs glasses now to help see things at a distance. She also happily offers that she still has most of her teeth.

As Perls was saying goodbye after his recent visit, Senhouse mentioned a friend of hers in California who is 102. Perls did a double-take.

“You have a friend who is 102?” he said. “Why didn’t I ever hear about this before?”

After securing a promise from Senhouse to ask her friend about enrolling in Perls’s study, he leaned over to give her a hug.

“Tell your wife,” Senhouse said saucily, “that there’s a 112-year-old in Wellesley that will give her a run for her money.”

For more information about the centenarians’ studies: 1-888-333-6327, e-mail [agewell@bu.edu](mailto:agewell@bu.edu), or visit [www.bumc.bu.edu/centenarian](http://www.bumc.bu.edu/centenarian) or [www.longevityomics.org](http://www.longevityomics.org).



Herlda Senhouse received a kiss from Adell Banks, 85, after they had lunch together Saturday, May 6 in Wayland. JESSICA RINALDI/GLOBE STAFF