THE PATIENT
Her mother had it; her sister has it; her brain could have early signs.

The Last Case

THE DRUG
The most promising lead yet on a cure

# of Alzheimer's

BY TK PHOTOGRAPHS BY ETHAN HILL

Rachelle Laliberte • 3/18/15, 4:26 PM

Alzheimer's is as much a part of Helene DeCoste's life as fall leaves and droll stoicism. Her mother lost her mind to the disease, and Helene cared for her until the end. Helene's older sister Judith was next; she no longer knows Helene's name. Helene herself may now have signs of the disease in her brain. Yet even as she shrugs off her seemingly inevitable fate, scientists down the road from her are testing an astonishing new drug. And she wonders: Could it change her family history for good?

Helene's mother, Helen Kelley, in the 1930s

Helene DeCoste senses the news could be bad before she and her husband, Russ, even take their seats in the doctor's office. Instead of the one neurologist they expected to see, there are two, and that can't be good. In a moment the couple will have the answer they've been waiting for, an answer that will determine a lot about Helene's future. About their future. The results of a recent scan will tell them whether her brain contains a telltale marker of Alzheimer's disease.

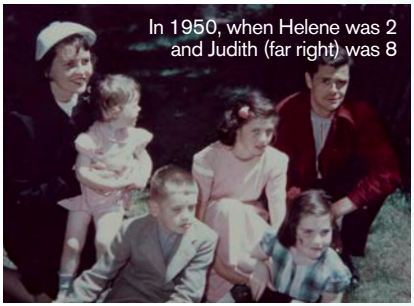
Bad news would not be a shock. Alzheimer's runs through Helene's family like fat marbling a steak, reaching invisibly into each generation. Her mother and an aunt both died from Alzheimer's-like dementia, and Helene's older sister Judith was diagnosed 4 years ago.

That family history is what brought Helene, 67, to this Boston neurology practice in the first place. She and hundreds of other patients across the United States, Canada, and Australia have volunteered to be screened for admission to a landmark study called Anti-Amyloid Treatment in Asymptomatic Alzheimer's, or the A4 study. While researchers may disagree about what causes the disease and how it might be

PHOTOGRAPHS COURTESY OF HELENE DECOSTE

treated in the future, they agree on this: The A4 could be the vital first step in finding our way out of this mess. Unlike any of the studies that have come before it, the A4 aims to prevent, or at least halt the progression of, changes in the brain that lead to this most feared and most common form of dementia—the very changes that Helene's brain may already have begun to show.

With her white hair and stately posture, Helene looks like a kinder, gentler Barbara Bush, one who's traded her suits for loose, colorful clothes. She'll tell you that of her three sisters, one got the beauty, one got the brains, and she got the common sense. The family's Alzheimer's nightmare began in earnest 25 years ago, when their father was hospitalized and they realized how impaired their mother, Helen, had become. "By then she was not capable of daily care," Helene says, her strong Boston accent turning *not* into *nawt*. It wasn't long before she no longer recognized her family. Helen died in a nursing home in 1993.

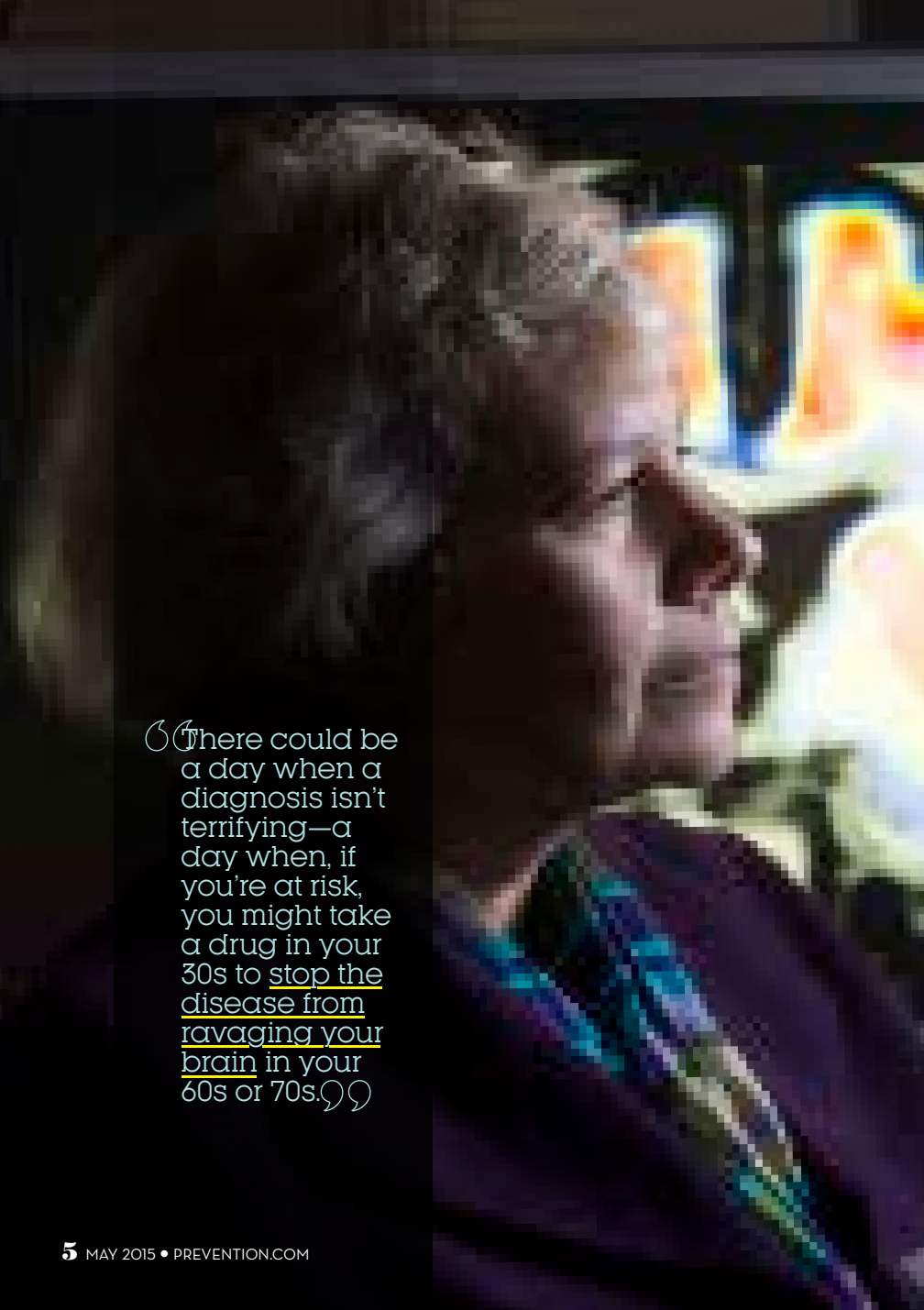

In 1950, when Helene was 2 and Judith (far right) was 8

Fourteen years after their mother's death, Helene noticed Judith doing some strange things. Once, after missing a grandnephew's birthday party,

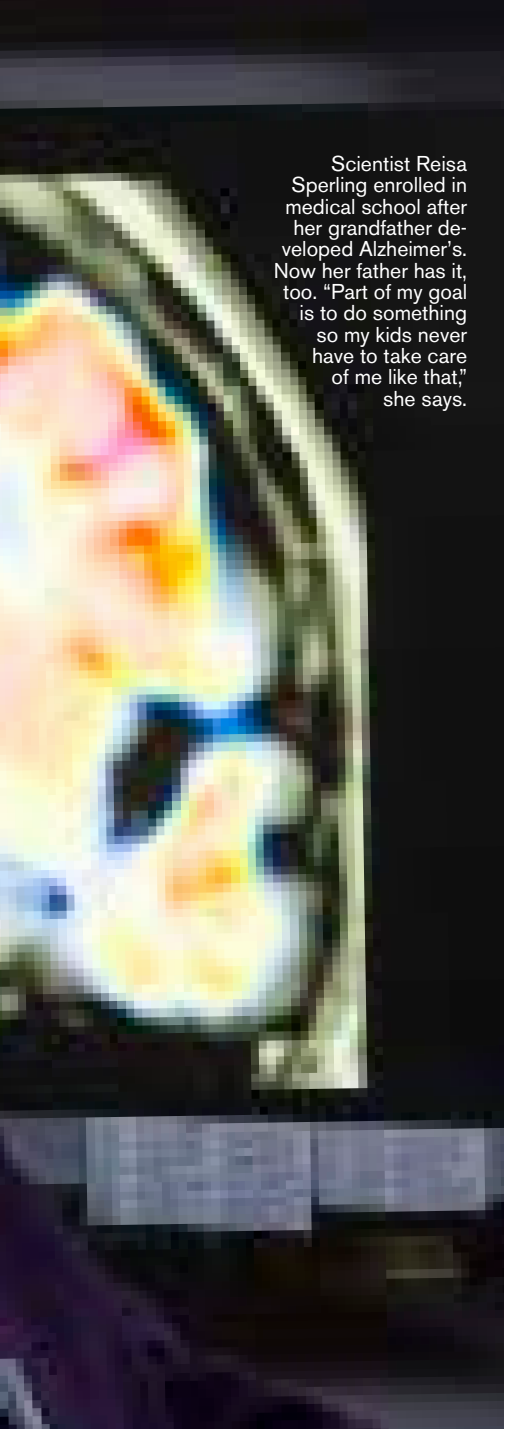

Judith, the "brains" of the family, and their mother, Helen, in 1967

Judith called to admit that she had driven to the wrong apartment and had no idea where she was. By early 2011, when Helene discovered thousands of pieces of unopened mail all over Judith's house, it was clear something was seriously wrong. Judith was diagnosed with mild cognitive impairment, a disorder that sometimes precedes Alzheimer's. But Helene worried that her sister was more than mildly impaired.

One morning that winter, a nurse making a home visit brought up the subject of assisted living. Rattled and angry, Judith went to the kitchen to make a cup of coffee—and mistakenly ground up cat food instead of coffee beans. ("You're allowed to laugh, because it's hysterically funny," Helene says.) The nurse called Helene, Helene



“There could be a day when a diagnosis isn’t terrifying—a day when, if you’re at risk, you might take a drug in your 30s to stop the disease from ravaging your brain in your 60s or 70s.”



Scientist Reisa Sperling enrolled in medical school after her grandfather developed Alzheimer's. Now her father has it, too. "Part of my goal is to do something so my kids never have to take care of me like that," she says.

called Judith's doctor, and soon Judith had an Alzheimer's diagnosis, prescriptions for Aricept and Namenda, and a doctor's note suggesting assisted living.

During those same early months of 2011, a team of scientists a few miles away was working on some paradigm-shifting research. Years of experimental protocols had produced Alzheimer's treatments that barely made a dent in symptoms and did nothing to cure or even slow the disease in patients who showed signs of cognitive trouble. Experts had regretfully concluded that the disease, once in progress, could not be treated. But in May 2011, the same team, led by Reisa Sperling, the director of the Center for Alzheimer's Research and Treatment at Brigham and Women's Hospital in Boston, published a study showing that physiological changes in the brain might be detectable before memory loss set in—what's known as the preclinical phase of the disease—opening up the possibility of slowing or reversing them before they truly take hold.

This bombshell was made possible by new imaging techniques that let researchers observe living brains in real time instead of having to wait until an autopsy revealed what lay inside the organs' gray matter. A healthy brain comprises 3 pounds of dense, compact, wrinkly grooves (known as sulci) and ridges (gyri) that look a bit like a neatly

wrapped gift. A cross section resembles a head of fresh cauliflower, its springy florets tightly packed together. A brain that's been decimated by Alzheimer's, on the other hand, looks like a package wrapped by a 5-year-old, with holes, shriveled ridges, and spaces gaping between the furrows and coils.

Helene's parents, Helen and John Kelley, got married in 1935.

Below the surface of the cerebral cortex lie more differences. Healthy neurons look something like starfish, constantly reaching toward other neurons with feathery dendrites and a long, rootlike axon. (The National Institute on Aging's website says, rather fancifully, "Neurons live to communicate with each other.") But the neurons in a brain with Alzheimer's are stuffed with snarls of misfolded proteins called tau, which obstruct the neurons' ability to communicate. They float among tumbleweed drifts of amyloid plaques, damaged proteins that cut them off from other cells. The more plaques and tangles accumulate in the brain, the more deeply people fall into blankness, losing memory, the ability to think, and, finally, all sense of themselves.

Helene says she's not scared by the prospect of developing Alzheimer's and doesn't dwell on it. "I could be hit by a car tomorrow," she says, shrugging. "I really can't think about Alzheimer's too much." But no one can really face that kind of prospect without emotion. And while Helene and Russ and their two adult daughters, Aimee and Rachelle, are philosophical when they talk about the future, there are moments when fear shines through. When Rachelle remembers her grandmother, Helen, years ago, deep into Alzheimer's and begging to see her long-dead brother, her blue eyes fill with tears. "I do feel concerned about my mom," Aimee says. "It's there in the back of my mind."

Clearly Helene worries about what her diagnosis could mean for her close-knit family. "Visiting my mother in the nursing home and watching her decline, going through all those emotional ups and downs, I used to tell my daughters, 'Shoot me if this happens to me,'" she says matter-of-factly. Her mother donated tissue from her brain to Alzheimer's research, and as her sister started to decline, Helene, too, felt a de-

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Siobhan Young • 3/18/15, 5:13 PM
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Helen, Judith, and Helene in the '80s. Helen likely was already dealing with the early effects of Alzheimer's.

In a corner of the dreary room sits
A woman feeble and worn by the years.
She glances at each of us who visits.
Inside she knows everyone deeply cares.
A woman who was once so much alive,
creativity did practice in her mind.
Quickly an awful disease did arrive.
Recently all that has seemed to unwind.
Why did this awful trait happen to her?
She had so much and forced she is to fall.
active that she did prefer,
er memory has become so small.
disease is taking her away.
efully for Nana everyday.

Helene's older daughter, Aimee, wrote the poem at right about her grandmother in 1989.

"My mother and her sister were the only two of a family of six children who lived beyond their 60s," Helene says, "so we don't know whether the others would have had Alzheimer's, too."

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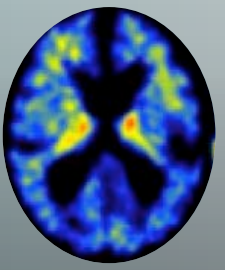
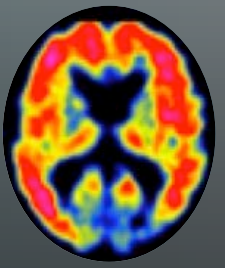
A Brain
on Alzheimer's

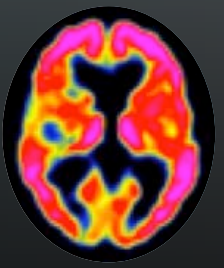
Or rather, on the amyloid plaques that can foreshadow dementia to come



A low level of amyloid plaques (in red) is a normal part of a healthy adult brain.



Volunteers in the A4 study have elevated amyloid, seen here, but aren't showing symptoms.



This patient has Alzheimer's dementia—and considerably elevated amyloid.

sire to help. So when, in 2013, she heard a radio plea for volunteers for the A4 study—which was being led by Boston researcher Reisa Sperling herself—Helene called the 800 number.

Nearly every Alzheimer's researcher in the country has gotten on board with recruiting patients for the A4 study. "It's incredibly exciting," says Anne M. Fagan, a professor of neurology at Washington University's School of Medicine in St. Louis. "The A4 and other studies on the horizon are the closest the field has come to assessing various drugs' effects before irreparable brain damage has taken place." This hopeful research couldn't be more timely, given that more than 75 million baby boomers have begun turning 65, when the likelihood of developing the disease escalates exponentially. "We have to do something or this will cripple our society," says Jessica Langbaum, a principal scientist at the Banner Alzheimer's Institute in Phoenix. "We won't have enough people to care for those with Alzheimer's—it will bankrupt our health care system."

A4 study participants whose scans show elevated amyloid will receive 3 years of monthly infusions of either a placebo or an experimental drug, solanezumab, which has been shown to help clear the brain of amyloid. The hope is that the drug will stop the plaques from proliferating. Solanezumab is what's

called a monoclonal antibody, designed to bind to a particular substance—in this case, amyloid-beta peptides, the main component of amyloid plaques. In mouse trials, solanezumab bonded with amyloids and moved them out of the brain, rendering them harmless. Recent studies on people with Alzheimer's found it slowed cognitive decline in those with the mildest signs. Researchers believe solanezumab may work best in people with amyloid plaques but no symptoms.

Amyloid plaques show up on PET (positron emission tomography) scans, which is one reason the A4 study targets them. (Newer techniques allow researchers to see tau protein building up in the brain, and the A4 study has just started to include tau PET imaging, too.) A certain level of amyloid is normal, but the higher the level, the higher the risk of Alzheimer's. Recent studies suggest that amyloid builds up in the brain years before symptoms appear. "It's analogous to cholesterol," says Sperling. "We know cholesterol builds up in arteries 20 years before people have a heart attack or stroke. If you can lower cholesterol, you can reduce heart disease. Imagine if we could reduce Alzheimer's dementia by using a similar approach."

If solanezumab does what it's supposed to, there could be a day when Alzheimer's isn't the terrifying diagnosis it is now—a day when, if you're at risk, you might take a drug in your 30s to stop the plaques from ravaging your brain in your 60s or 70s.

Helen in her 20s, in the early 1930s

PHOTOGRAPH COURTESY OF HELENE DECOSTE

The pursuit of that promising future is precisely what put the DeCostes in the Boston neurologist's office last winter, facing doctors who were recruiting patients for the A4 study. Two of them. Helene listened quietly as one explained that her brain has elevated amounts of amyloid plaques. She and Russ felt calm. They'd had nearly three decades to brace themselves for this.

The results qualified Helene for the A4 study, and she immediately agreed to participate. "Recently I had a conversation with my deceased parents—and I'm not like that," she says with a laugh. Then she turns serious. "I said to them 'You've been through this, so you're gonna help me.' I believe they're up there sending me signals and that I'm doing what I'm supposed to be doing."

The A4 is a double-blind study, so no one knows who's getting the antibody and who's not. If Helene ends up with the placebo, she'll be invited to take solanezumab after the trial ends. Should she develop symptoms, she'll get referrals to top specialists. She sees this as a bonus whether she develops Alzheimer's or not. Her optimism doesn't come from some kind of Pollyanna outlook, she says; she's simply been living with the possibility for a long time now. "If it does happen, I don't know when that will be," she says. "How do you prepare for something like that? Going into this study is my way of dealing with it."

It's Pie Day at Bridges Memory Care, and Helene is here visiting her sister Judith, as she has for the craft fairs and luaus and pretty much every other family activity at this Hingham, MA, facility. A man with a gray ponytail plays easy listening tunes on a guitar as families spoon pie off paper plates.

Judith's long-term prognosis is both familiar and bleak. But today is a good day, and one thing Helene has learned is that with Alzheimer's, as with everything, the present moment is all there is. So she sits beside her sister, both of them eating pie, and when the guitar player swings into "You Are My Sunshine," they turn to each other and begin to sing. In profile they look even more like sisters, with their short silvering hair and warm blue eyes. "You are my sunshine, my only sunshine," they sing, smiling at each other. "Please don't take my sunshine away."

The Bridges activities director, an energetic young woman, rushes over with a camera to capture the tableau. Then she's off, greeting another family. The conversation at the table turns to movies. "Did we see *Jaws*?" Helene asks Russ.

"We saw it in New York City. You don't remember?" says Russ. There's a pause, then he says quickly, "That's right, you weren't there." A palpable sigh of relief flows around the table. There are moments now when Aimee, Rachelle, and Russ freeze up, catch each other's eyes, and wordlessly wonder if this is it, if this is the beginning. The answer, for today, is still no.

The guitar player shifts into a new melody. Judith listens, then elbows Helene, tilting her head as if to say *Get a load of this.* After a second Helene laughs out loud, and so does Judith, as the unmistakable notes of "If I Only Had a Brain" from The Wizard of Oz purl through the room. "She gets it. She thinks it's funny," whispers Helene. As Judith laughs and laughs, the look on Helene's face suggests it's some kind of victory. Maybe it is.

"I see her slipping in little ways," Helene says of her sister Judith, "but the doctor says she's doing well."

"If I do get Alzheimer's, I don't know when it'll happen,' Helene says. 'How do you prepare for something like that? Going into this study is my way of dealing with it."