In better years, Cesiah Lane loved numbers, a great meal and any chance to dance. But her life changed dramatically within a few years of celebrating her 80th birthday. She could no longer balance a checkbook, she ate the same simple meals every day, and she chose to stay close to her home in Los Angeles.

But it was only when Laura Crockett, her daughter, received a long-distance call from her mother that she knew something was terribly wrong in her mother’s brain. “What’s a home equity loan?” her mother wanted to know. In better years, Lane ran a successful import-export brokerage firm. She owned her home, outright. Of course she knows what a home equity loan is, her daughter thought.

And then she remembered her mother’s puzzling family history. Three of Lane’s six sisters died of Alzheimer’s disease.

Lane would become the fourth member of her close-knit family to be diagnosed with Alzheimer’s disease. In 2007,
when she was 83, doctors at the University of Southern California (USC) in Los Angeles told her that she had mild Alzheimer’s disease. Three years later, her short-term memory was already stripped away. She died last March.

In death, Lane left her brain to the doctors who took care of her in life. She had been part of a few clinical studies at the university, and she had agreed to an autopsy that might help scientists figure out the disease that wiped out a generation of sisters.

Autopsied brain tissue has literally led to most of the major findings in Alzheimer’s disease. Alois Alzheimer was a psychiatrist and neuropathologist who in 1901 began treating a 51-year-old woman named Auguste Deter who had exhibited a number of strange behaviors at an asylum in Germany. Deter died five years later, and Alzheimer took her brain to a laboratory where he used state-of-the-art staining techniques to look inside the folds of her brain tissue. There, he would note what today is commonly known as the hallmark pathology of the brain disorder: plaques and tangles.

It would be another 50 years before a team of British physicians conducted the first large-scale autopsy study of elderly people that revealed that plaques and tangles are not a rare event. Rather, they are common in the aging brain. The more pathological footprints, the more likely the person had been living with Alzheimer’s disease.

Since, with more detective work on autopsied brain tissue and with today’s more advanced pathological techniques, scientists have learned that there may well be distinct subtypes of dementia—Alzheimer’s disease, Lewy-body damage (also in Parkinson’s disease) and vascular disease.

“We wouldn’t be able to talk about any of this without autopsy material,” said Thomas Bird, M.D., a professor of medicine, neurology and medical genetics at the University of Washington in Seattle. “This information has very practical implications. Scientists need to know what is wrong with the brain to accurately develop effective treatments.”

And finally, Bird said, while clinical judgment on the search for a diagnosis in the best of hands—those who specialize in the care of people with Alzheimer’s disease—may be 90 percent, the accuracy of a diagnosis among physicians without this expertise is about 70 percent. The only way to confirm a true diagnosis of Alzheimer’s disease is through a brain autopsy.

Again, research helps tell the story. What has become very clear from these studies is that what may look like Alzheimer’s disease is very different once the brain is broken open to reveal its secrets.

A long-term study involving the School Sisters of Notre Dame has forever changed how we think about Alzheimer’s disease. In 1992, nearly 700 older nuns in the order throughout the Eastern, Midwestern and Southern regions of the United States signed on to a longitudinal study at the University of Minnesota and agreed to donate their brains to researchers upon death. The nuns, aged 75 to 102 at the study’s onset, were evaluated every year for dementia so the scientists knew when memory and cognitive problems emerged. Those who are still alive are still getting these work-ups. And at death, researchers were able to connect what they knew about each woman to the story her brain pathology would tell.

Having such a large sample of people over decades and then having the autopsies at the end of the road is invaluable to science. There have been surprises. A third of the brains in nuns who were thought to have Alzheimer’s disease did not have the mind-robbing disease. And there were many who had all of the pathological signs of the disease but had no signs of cognitive trouble while alive.

It was the nuns who showed us that the disease begins decades before the first clinical signs, said James Mortimer, Ph.D., a professor of epidemiology at the University of South Florida in Tampa who collaborated on the study. The autopsied brains also enabled scientists to figure out that the women with small head sizes had significantly lower educational achievement in early adult life.

“If you only look at clinical outcomes you are looking at part of the story,” said Mortimer.

For instance, let’s take APoe4, a gene variant that increases the risk for late-onset Alzheimer’s disease.
We inherit one copy of the APOe gene from both of our parents. There are three variants, or alleles, that you can inherit: an e2, e3 and e4. In 1993, scientists discovered that people with one copy of the e4 allele are four times at higher risk of Alzheimer's disease than those without this allele. Two copies and you are 10 to 15 times more likely to develop it.

But what the nun study tells us is that the brains of people with e4 do have a severe pathology that is indicative of Alzheimer's disease, but there were many nuns who did not have Alzheimer's disease.

It speaks to this idea that “people have reserve capacity and that is covering up the disease,” Mortimer suggested.

The autopsied brain is also beginning to help scientists assess the effectiveness of therapies on the disease pathology.

The Honolulu-Asia Aging Study conducted in the 90's at the University of Hawaii looked at the pathology of brains of 285 older Asian men. The study results would negate the belief that doctors are dealing with one neurodegenerative disorder. The researchers divided the autopsied brains into six subsets based on the tissue's primary pathology, including microvascular lesions, Alzheimer's lesions, hippocampal scarring and Lewy-bodies. What they discovered was that while 53 percent of the men had symptoms of Alzheimer's disease, only 12 percent of the brains showed Alzheimer's lesions.

“In life, for now, none of these conditions can be distinguished from Alzheimer's disease,” said Lon White, M.D., a professor of geriatric medicine who led the study. “Just calling it Alzheimer's disease doesn't help us know what the person has going on in their brain.”

The question is this: Will you donate? If so, why? And if yes, how do you go about it?

In the longest-running study of its kind, researchers at the Group Health Research Institute in Seattle and the University of Washington have been tracking a group of older people since 1994; the Adult Changes in Thought (ACT) study enrolls about 240 people a year, keeping the pool fixed at about 2,000 subjects. The participants are asked initially or throughout the study whether they would consider a brain autopsy. If they say “yes,” they are asked to fill out consent forms. Eventually, 50 percent of the subjects become donors. The institute now has 500 brains on ice.

The donors come with a short list of reasons. Some people want to understand their own familial risk, with the thought of possibly undergoing genetic testing or making lifestyle changes. Others seek a sense of closure. And still others feel it is a way to give back to science.

Crockett, who lives in Trenton, NJ, wanted to know what exactly changed her mother from a high-powered working woman who loved a good party (with dancing, of course) to a woman who couldn't remember that she had oatmeal, bananas and hot milk two or three times a day.

“If not my mother, then who?” Crockett said. “If they can learn something about Alzheimer's from my mother's brain that would be fantastic.”

While people can donate their brain to science, some have found the process overwhelming. It is getting easier with a growing number of brain banks or tissue resource centers. Currently, there are about 65 in the United States, according to the International Brain Banking Network; these brain banks collect, store and distribute tissue to neuroscientists worldwide.

Research institutes studying neurodegenerative diseases like Alzheimer's also have brain autopsy programs. Lane had been part of several medication trials at the USC, one of 27 federally-funded Alzheimer's Disease Centers (ADCs) across the country. Many ADCs offer brain donation programs. Simply call up the investigators and ask whether they have studies that accept brain donations for postmortem research.

In addition, the National Institutes of Health plans to start a campaign to educate the public and develop a sort of one-stop shopping for brain bank donations called NeuroBio Bank. A Web site should be up and running next spring that will have details on how to donate and contact information for brain banks in the United States, said A. Roger Little, Ph.D., senior advisor for the National Institute of Mental Health's (NIMH) science policy planning and communications office.

According to Little, anyone interested in donating a
Search Here for Brain Banks/Research Studies

Alzheimer’s Disease Centers—National Institute on Aging
http://www.nia.nih.gov/alzheimers/alzheimers-disease-research-centers
800.438.4380

International Brain Banking Network

National Institute of Neurological Disorders and Stroke
800.352.9424

ClinicalTrials.gov—National Institutes of Health
www.clinicaltrials.gov

brain can call a brain bank and sign up. This includes people with healthy brains, which act as “normal controls” to compare with diseased tissue in studies. “Healthy brains are just as critical for research as diseased brains,” he said.

The typical protocol is straightforward: A brain donor will be asked to sign a consent form and then be given information for next of kin or a legal representative so this person knows what to do with the deceased body. Brain donors can also make their intentions known in a living will or advanced directive.

Researchers work with medical examiners and hospital pathologists so if they know in advance about a brain donation, coordinators can help make arrangements with the family. When a loved one passes, the family calls the designated phone number, and the receiving institution or a courier service picks up the body for autopsy. The research institute coordinates the autopsy and the delivery of the body to the funeral home after the tissue is removed.

Brain tissue must be procured quickly. Researchers must receive the brain generally within three to eight hours of a person’s death if the tissue is going to be frozen for use in biochemical studies. (Proteins and chemicals deteriorate quickly if the proper oxygenation and temperature is not maintained.) But if the tissue is targeted for other types of studies the medical examiner or pathologist can often still receive the donation within a day or two. (Plaques and tangles don’t change.)

Within minutes of Lane’s passing at home, her daughter, who had been taking care of her for several years, was prepared with the cell phone number of a nursing coordinator at USC. The brain bank programs work round-the-clock. Lane’s body was transported to the USC pathologists, and within seven hours of Crockett’s call, they began the process of collecting brain specimens.

As is the way with brain autopsy, the process is not disfiguring. The brain is removed through a small incision in the back of the head.

There is no charge for a brain donation and often the medical examiner, pathologist or researcher will share the information from the autopsy with the person’s family. The number of brains of people who have been diagnosed with Alzheimer’s disease that come to autopsy is relatively small, White said. The majority of the brains procured are for research purposes. (Some people request an autopsy to confirm a diagnosis.) And for good reason, experts say. People enrolled in a research study do not have to pay for the autopsy, which can cost a few thousand dollars and is not covered by insurance. Of course, people do not have to join a research study to have a brain autopsy. They can pay for it.

What is important is that the brain ends up in the hands of a pathologist with an expertise in Alzheimer’s disease, said University of Washington’s Bird. Alternatively, if your loved one dies in a hospital, you can request an autopsy. Hospitals by law must comply with the request and absorb the hefty cost of the autopsy. But be warned: the hospital pathologist is probably not an expert on Alzheimer’s disease and might not be able to distinguish the possible subtypes that led to the dementia, said Bird.

Crockett received the results of her mother’s autopsy several months after it was performed. Her brain showed sparse diffuse plaques in the areas hard hit by Alzheimer’s disease: the hippocampus, entorhinal cortex and the frontal and temporal lobes.

“Just knowing is important to me,” said Crockett. She said she also plans to donate her brain to science when she dies.

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