

December 26, 2007

SIX KILLERS: ALZHEIMER'S DISEASE

Finding Alzheimer's Before a Mind Fails

By [DENISE GRADY](#)

For a perfectly healthy woman, Dianne Kerley has had quite a few medical tests in recent years: [M.R.I.](#) and PET scans of her brain, two spinal taps and hours of [memory](#) and thinking tests.

Ms. Kerley, 52, has spent much of her life in the shadow of an illness that gradually destroys memory, personality and the ability to think, speak and live independently. Her mother, grandmother and a maternal great-aunt all developed [Alzheimer's disease](#). Her mother, 78, is in a [nursing](#) home in the advanced stages of [dementia](#), helpless and barely responsive.

"She's in her own private purgatory," Ms. Kerley said.

Ms. Kerley is part of an ambitious new scientific effort to find ways to detect Alzheimer's disease at the earliest possible moment. Although the disease may seem like a calamity that strikes suddenly in old age, scientists now think it begins long before the mind fails.

"Alzheimer's disease may be a chronic condition in which changes begin in midlife or even earlier," said Dr. John C. Morris, director of the Alzheimer's Disease Research Center at [Washington University](#) in St. Louis, where Ms. Kerley volunteers for studies.

But currently, the diagnosis is not made until symptoms develop, and by then it may already be too late to rescue the brain. Drugs now in use temporarily ease symptoms for some, but cannot halt the underlying disease.

Many scientists believe the best hope of progress, maybe the only hope, lies in detecting the disease early and devising treatments to stop it before brain damage becomes extensive. Better still, they would like to intervene even sooner, by identifying risk factors and treating people preventively — the same strategy that has markedly lowered death rates from heart disease, [stroke](#) and some cancers.

So far, Alzheimer's has been unyielding. But research now under way may start answering major questions about when the disease begins and how best to fight it.

A radioactive dye called PIB (for Pittsburgh Compound B) has made it possible to use PET scans to find deposits of amyloid, an Alzheimer's-related protein, in the brains of live human beings. It may lead to earlier diagnosis, help doctors distinguish Alzheimer's from other forms of dementia and let them monitor the effects of treatment.

Studies with the dye have already found significant deposits in 20 percent to 25 percent of seemingly normal people over 65, suggesting that they may be on the way to Alzheimer's, though only time will tell.

"PIB is about the future of where Alzheimer's disease needs to be," said Dr. William E. Klunk, a co-discoverer of the dye at the Alzheimer's research center at the [University of Pittsburgh](#). "PIB is being used today to help

determine whether drugs that are meant to prevent or remove amyloid from the brain are working, so we can find drugs that prevent the underlying pathology of the disease.”

Though PIB is experimental now, studies began in November that are intended to lead to government approval for wider use.

Currently, for the most common form of Alzheimer's disease, which occurs after age 65, there is no proven means of early detection, no definitive genetic test. But PIB tests might be ready before new treatments emerge, making it possible to predict who will develop Alzheimer's — without being able to help.

Researchers are also using M.R.I. scans to look for early brain changes, and testing blood and spinal fluid for amyloid and other “biomarkers” to see if they can be used to predict Alzheimer's or find it early.

Studies of families in which multiple members have dementia are helping to sort out the genetic underpinnings of the disease.

Finally, experiments are under way to find out whether drugs and vaccines can remove amyloid from the brain or prevent its buildup, and whether doing so would help patients. The new drugs, unlike the ones now available, have the potential to stop or slow the progress of the disease. At the very least, the drug studies will be the first real test of the leading theory of Alzheimer's, which blames amyloid for setting off a chain of events that ultimately ruin the brain.

Some scientists doubt the amyloid theory, but even a staunch skeptic said the studies were important.

Among the skeptics is Dr. Peter Davies, a professor at [Albert Einstein](#) Medical College, who said: “You've got to try. Somebody's going to get this right.”

But if the amyloid hypothesis does not hold up, much of Alzheimer's research could wind up back at Square 1.

Answers are urgently needed. Alzheimer's was first recognized 100 years ago, and in all that time science has been completely unable to change the course of the disease. Desperate families spend more than \$1 billion a year on drugs approved for Alzheimer's that generally have only small effects, if any, on symptoms. Patients' [agitation](#) and [hallucinations](#) often drive relatives and [nursing homes](#) to resort to additional, powerful drugs approved for other diseases like [schizophrenia](#), drugs that can deepen the oblivion and cause severe side effects like [diabetes](#), stroke and movement disorders.

Alzheimer's is the most common cause of dementia (artery disease, [Parkinson's](#) and other brain disorders can also lead to dementia). Five million people in the United States have Alzheimer's, most of them over 65. It is the nation's sixth leading cause of death by disease, killing nearly 66,000 people a year and probably contributing to many more deaths. By 2050, according to the Alzheimer's Association, 11 million to 16 million Americans will have the disease. “Sixteen million is a future we can't countenance,” said William H. Thies, the association's vice president for medical and scientific relations. “It will bankrupt our health care system.”

The costs are already enormous, \$148 billion a year — more than three times the cost of chronic [lung disease](#), even though Alzheimer's kills only half as many people. To a great extent, increases in dementia are the price of progress: more and more people are living long enough to get Alzheimer's, some because they survived heart disease, strokes or [cancer](#). It is a cruel trade-off. The disease is by no means inevitable, but among people 85 and older, about 40 percent develop Alzheimer's and spend their so-called golden years in a thicket of [confusion](#), ultimately becoming incontinent, mute, bedridden or forced to use a wheelchair and completely

dependent on others.

“It makes people wonder whether they really want to live that long,” Dr. Klunk said.

The potential market for prevention and treatment is enormous, and drug companies are eager to exploit it. If a drug could prevent Alzheimer's or just reduce the risk, as statins like [Lipitor](#) do for heart disease, half the population over 55 would probably need to take it, Dr. Thies said.

If new drugs do emerge, they will come from studies in patients who already have symptoms, Dr. Thies said. But he said the emphasis would quickly shift to treating people at risk, before symptoms set in. Many researchers doubt that even the best preventive drugs will be able to heal the brains of people who are already demented.

Treating preventively, Dr. Thies said, “will be more satisfying to patients and physicians, and there will be an economic incentive because you'll wind up treating more people.”

The only thing that could slow the drive for early treatment, he said, would be serious side effects — and Dr. Morris, at Washington University, said drugs powerful enough to treat Alzheimer's would probably have strong side effects.

Researchers are especially eager to study people like Ms. Kerley, because the children of Alzheimer's patients have a higher-than-average risk of dementia themselves, and tracking their brains and minds may open a window onto the earliest stages of the disease.

“I want to do anything I can possibly do to help find a cure or find a way to identify it earlier,” Ms. Kerley said. “We need to stop this. I don't know if it will help my generation, but it will help my son's.”

She figures that being a research subject may have advantages, too.

“We're the first ones in line,” she said. “If I am genetically predisposed, and they have a preventive medication, they'll tell me right away.”

Alzheimer's Beginnings

Some [forgetfulness](#) is normal. Distraction, [stress](#), fatigue and medications can contribute. A joking rule of thumb about Alzheimer's is actually close to the truth: it's O.K. to forget where you put your car keys, as long as you remember what a key is for. But worsening forgetfulness is a cause for concern.

Doctors use standard memory and reasoning tests to diagnose dementia, along with symptoms reported by the patient and family members. The term “mild cognitive impairment” is sometimes applied to small but measurable memory problems. But its meaning is unclear: some studies find that the impairment can resolve itself, while others suggest that it always progresses to dementia.

Even if older patients think more slowly or take longer to remember, as long as they can still function independently, they are not demented, Dr. Morris said.

In her heart, Ms. Kerley suspects that her mother's Alzheimer's disease began long before the official diagnosis in 2001 or even the tentative one in 1995 — years before, maybe decades. She wonders if the disease might explain, at least in part, her mother's difficult personality and lack of interest in reading or education.

When does Alzheimer's begin? The question haunts families and captivates scientists.

Dr. Morris said, "We think that by the time an individual begins to experience [memory loss](#), there is already substantial brain damage in areas critical to memory and learning."

No one knows whether the disease affects thinking, mood or personality before memory fails. Researchers think that the brain, like other vital organs, has a huge reserve capacity that can, at least for a time, hide the fact that a disease is steadily destroying it.

"I'm speculating that it does affect you throughout life," said Dr. Richard Mayeux, a professor of neurology, [psychiatry](#) and epidemiology at [Columbia University](#), and co-director of its Taub Institute for Research on Alzheimer's Disease and the Aging Brain. "I think there's a very long phase where people aren't themselves."

If Dr. Mayeux asks family members when a patient's memory problem began, they almost always say it started a year and a half before. If he then asks when was the last time they thought the patient's memory was perfectly normal, many reply that the patient never really had a great memory.

Several studies in which people had intelligence tests early in life and were then evaluated decades later have found that compared with the healthy people, those with Alzheimer's had lower scores on the early tests.

"It raises the possibility for me that this is a genetic disorder that starts early in life," Dr. Mayeux said.

He said those findings also made him wonder about the widely dispensed advice to read, take courses, solve puzzles and stay mentally active to ward off Alzheimer's. The advice is based on studies showing that highly educated people have a lower risk of Alzheimer's than do less-accomplished ones. But does that mean that mental activity prevents Alzheimer's — or vice versa?

'I Have Lost Myself'

The disease is named for Alois Alzheimer, a German doctor who first described it in Auguste D., a 51-year-old patient he saw in 1901. Her memory, speech and comprehension were failing, and she suffered from hallucinations and paranoid delusions that her husband was unfaithful. Unable to finish writing her own name, she told Alzheimer, "I have lost myself."

She died in 1906, "completely apathetic," curled up in a fetal position and "in spite of all the care and attention," suffering from bedsores, Alzheimer wrote.

A century later, patients still die in much the same way. Although Alzheimer's itself can kill by shutting down vital brain functions, infections usually end things first — [pneumonia](#), bladder infections, [sepsis](#) from bedsores.

When Alzheimer dissected Auguste's brain, he found it markedly shrunken, a wasteland of dead and dying nerve cells littered with strange deposits.

There were two types of deposits, plaques and tangles. Plaques occur between nerve cells, and are now known to consist of clumps of beta amyloid, an abnormal protein. Tangles form inside nerve cells, and are made of a protein called tau that is normally part of a system of tubules that carry nutrients to feed the cell. Once tau is damaged, the nerve cells essentially starve to death.

Until the 1970s Alzheimer's disease was considered a rare brain disorder that mysteriously struck younger

people like Auguste D.

It was thought to be different from “senility,” which was assumed to be a consequence of aging. But then researchers compared the brains of younger people who had died of Alzheimer’s with those of elderly people who had been senile, and discovered the same pathology — plaques and tangles. Senility, they decided, was not a natural part of aging; it was a disease.

The Amyloid Hypothesis

The leading theory of Alzheimer’s says that beta amyloid, or A-beta, is the main culprit, building gradually in the brain over decades and short-circuiting synapses, the junctions where nerve cells transmit signals to one other. Gradually, the theory goes, the cells quit working and die.

Everybody produces A-beta, but its purpose is not known. People who develop Alzheimer’s either make too much or cannot get rid of it. Although scientists once blamed plaques for all the trouble, more recent research suggests that the real toxins are smaller bundles of A-beta molecules that form long before plaques do.

Dr. Dennis J. Selkoe, a professor of neurologic diseases at [Harvard](#), said that just as lowering [cholesterol](#) can prevent heart disease, lowering A-beta may prevent Alzheimer’s or slow it, particularly in the early stages — provided that drugs can be created to do the job.

Several drugs and vaccines are now being tested that either block the production of A-beta or help the body get rid of it.

Researchers are also testing anti-amyloid [antibodies](#), which are proteins made by the immune system, as well as blood serum that contains the antibodies.

Eventually, Dr. Selkoe said, screening tests for Alzheimer’s “will be like getting an EKG in the doctor’s office at 45 or 50, and you’ll start treating right away to prevent Alzheimer’s rather than treat it.”

Other researchers are less enthusiastic, noting that there have been numerous failures and disappointments along the way. A vaccine study had to be halted in 2002 because 18 of 300 patients developed [encephalitis](#), and 2 died. Some scientists worry that anti-amyloid vaccines in general could be dangerous, in part because the role of amyloid is not well understood and the brain may actually need it.

No Choice but to Cope

Even if current research yields new drugs, there is not likely to be a miracle pill that will bring people back from deep dementia. For now, there is no choice but to cope with the disease. Seventy percent of Alzheimer’s patients are cared for at home, and millions of families are struggling to look after them, piecing together a patchwork of relatives, friends, paid health aides and adult day-care programs.

Barbara Latshaw, 79, lives with her husband, David, and her sister in Crafton, Pa., near Pittsburgh. Ms. Latshaw, whose dementia was diagnosed in 1991, has not spoken in four years, and she can no longer smile. But she locks eyes with visitors and will not let go.

“There is still something alive in there,” said her sister, Fritzie Hess, 69. “I’m convinced of it.”

The family believes that, at least some of the time, she still understands them. They speak to her as if she does. She is with them, and yet gone, and they miss her terribly.

“We hope to keep her here at home until she passes on,” Ms. Hess said. “She’s a joy to us.”

Many families hope to keep Alzheimer’s patients at home, but not all can manage it, especially if family members have to go work or patients become combative, incontinent, immobile or unable to sleep at night.

“There are three of us taking care of my sister, and it works out beautifully,” Ms. Hess said. “We spell each other. I don’t know how these spouses manage, when it’s one on one.”

Ms. Hess and her brother-in-law are retired, and Ms. Latshaw’s daughter, Becky Bannon, 53, is free to visit many mornings to help them get her mother out of bed, massage and exercise her arms and legs, change her diaper and dress and feed her.

Ms. Latshaw used to be full of life. She loved to cook, played tennis and bridge, raised two children and took charge of redecorating the grand old family home. Then her memory began to slip: guests would arrive for dinner, and she would have no memory of inviting them. She forgot to look before pulling into traffic, and nearly caused an accident. She would wander out of the house, and local store clerks would take her home. She never turned hostile or angry, as many demented patients do, but she had vivid hallucinations of strings being caught in her teeth, and little men getting into her bed and jabbing her with broom straws. On especially bad nights, her husband would get up with her at 2 or 3 a.m. and make the two of them hot chocolate.

Aricept, an Alzheimer’s drug, made the hallucinations worse, while another drug, an antipsychotic used for schizophrenia, seemed to quell them. But the second drug had side effects: after taking it for several years, Ms. Latshaw began to grind her teeth, and could not stop moving her arms and legs.

Their father also suffered from dementia, Ms. Hess said, admitting that she wonders about herself.

“Naturally I’m a little bit concerned, but I think worry is such a waste of time, so I don’t dwell on it; I just don’t,” she said. “My friends always said, ‘You always had a bad memory.’ I see Barbara and David’s children having that same kind of memory.”

Ms. Hess has volunteered for studies at the University of Pittsburgh Medical Center, where she became the first person in the United States to have a PIB study of her brain.

“I’m very anxious to get to the bottom of this whole Alzheimer’s thing,” she said.

Nothing Left to Give

In an interview in the summer of 2006, Ms. Kerley described her mother this way: “She’s completely withdrawn in herself. She hasn’t recognized us for a few years. Basically she hums one line of one song over and over again. She seems to be stuck somewhere in her life between age 4 and 5.”

Ms. Kerley said she and her son Michael, then 21, visited every week or two.

“She loves getting her back rubbed, being smiled at, being hugged,” Ms. Kerley said. “She doesn’t know who we are. We’re going for us, not for her, because she doesn’t remember us the minute we walk out the door.”

She had signed her mother up for [hospice care](#) at the nursing home, meaning that she would receive medical care to keep her comfortable but no extraordinary measures like resuscitation if she began to fail. She said her mother would not want to be kept alive in her present condition.

“She has nothing left to give the world, and the world has nothing left to give to her,” Ms. Kerley said.

Nearly a year and a half later, her mother is still alive, even though Ms. Kerley has declined liquid nutritional supplements, [antibiotics](#) and [flu](#) and pneumonia shots.

Her mother does not even hum anymore, and spends much of her time in a fetal position, except when she is at the dinner table. She can still walk, if led.

“If my mother had her own choice, she would have offed herself a long time ago,” Ms. Kerley said. “There is no quality to her life.

“When she does go, it will be a blessing.”

Ms. Kerley has already arranged to donate her mother's brain and her own to Washington University. She seriously doubts that she will develop Alzheimer's. She is more like her father than her mother, she said, and she is the most educated person in her family, reads constantly and stays in shape by swing dancing two to five nights a week. And her students keep her sharp.

“If you want to keep up with me until you retire, that's fine,” she said. “I'm betting I'm not going to have that problem.”

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