

DISCOVERING ALZHEIMER'S BEFORE A MIND FAILS

DENISE GRADY .New York Times News Service

For a perfectly healthy woman, Dianne Kerley has had quite a few medical tests in recent years: MRI and PET scans of her brain, two spinal taps and hours of memory and thinking tests.

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," Kerley said.

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 Kerley volunteers for studies.

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 MRI 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 currently 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 Square1.

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 (pronounced thees), 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," 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, Thies said.

If new drugs do emerge, they will come from studies in patients who already have symptoms, 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, 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 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 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.

Kerley, a special-education teacher, has volunteered for various studies, including one that uses PET scans and the new dye that sticks to amyloid deposits in the brain.

"I want to do anything I can possibly do to help find a cure or find a way to identify it earlier," 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 OK to forget where you put your 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, Morris said.

In her heart, 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.

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 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," 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?