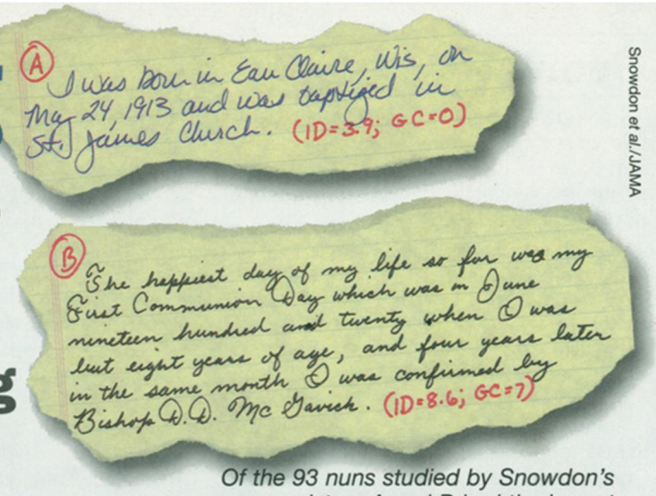
# Forecasting Alzheimer's Disease

## Brain scans and writing samples may predict dementia

By KATHLEEN FACKELMANN




Snowdon et al./JAMA

*Of the 93 nuns studied by Snowdon's group, sisters A and B had the lowest and highest scores, respectively, for the number of ideas in a given passage. Sister A's writing reflects a reliance on dates and names, a phenomenon common among nuns who would later develop Alzheimer's disease.*

First, there was a subtle, almost imperceptible, switch to simpler language. As time went on, the woman started using short phrases. Then, she could utter only a word. In the end, even that stopped.

That progression describes one of the most destructive aspects of Alzheimer's disease: the patient's loss of language.

The most common form of senility in people age 65 and older, Alzheimer's is a degenerative brain disease that often starts with mild forgetfulness. Indeed, it's difficult to distinguish early stages of Alzheimer's from normal memory lapses. Neurologists diagnose Alzheimer's dementia only after observing a pattern of ever-worsening cognitive problems, eventually including an inability to reason.

Two scientific reports now suggest that doctors may one day be able to identify healthy people who will develop Alzheimer's disease. In one study, researchers discovered that characteristics of a person's writing early in life appear to predict the disease. In the other, scientists demonstrate that a brain scan highlights changes that may precede dementia.

Do such procedures offer a practical test for Alzheimer's disease? Not now, says Steven T. DeKosky, director of the Alzheimer's disease research center at the University of Pittsburgh Medical Center. He also questions the value of such a test.

"We have no treatment for the disease," he notes. "What good does it do for someone to find out at age 45 that they have a chance of developing the disease?"

Yet he believes the recent findings will help researchers searching for ways to prevent Alzheimer's disease.

One team turned to a surprising set of subjects for its study—the Roman Catholic School Sisters of Notre Dame. In many ways, though, the sisters make ideal research subjects. Because they all have a similar lifestyle, environmental factors that might otherwise confuse the results of an Alzheimer's study are minimized or eliminated.

More important, this religious group keeps detailed, decades-long records on its members. These archives proved invaluable to David A. Snowdon of the University of Kentucky in Lexington and his colleagues in their study of aging and dementia.

The researchers knew that Alzheimer's disease leads to progressive impairment of language, and they wondered if subtle signs of difficulty would appear early in life. To find out, they studied 93 nuns whose handwritten autobiographies were on file in the convent archives. The autobiographies had been written as part of their religious training at an average age of 22. At the time of the study, these nuns were age 75 and older.

Team members looked at the number of ideas expressed in a passage of text, a concept called idea density. In addition, they studied the grammatical complexity of each autobiography. They then gave the elderly sisters a battery of tests that measure memory, concentration, language ability, and other cognitive skills.

Nuns whose autobiographies received the lowest scores in the idea density category were more likely than high-scoring nuns to perform poorly on cognitive tests. Low-scoring nuns were 30 times as likely as the high scorers to flub the Mini-Mental State Exam, a standard test of cognitive function.

When the investigators looked for links between grammatical complexity and Alzheimer's disease, they found only a weak association.

Snowdon's team knew that studies by other groups had indicated that education protects against Alzheimer's dementia, perhaps by building up a cognitive reserve early in life that offsets the disease process. To rule out education as a confounding factor, Snowdon's team repeated its analysis with a subgroup of highly educated sisters. In that group, low idea density also predicted dementia and Alzheimer's disease.

Finally, Snowdon's group took a close look at the brains of 14 sisters who had died since the study began in 1991. On the basis of autopsy results and earlier cognitive testing, the team confirmed a diagnosis of Alzheimer's in 5 of the 14. These women exhibited the neurofibrillary tangles typical of the disease. Tangles consist of twisted threads of protein thought to destroy the brain's nerve cells.

The autobiographies of all five of the sisters with Alzheimer's disease showed low idea density. In contrast, this linguistic marker did not characterize the writings of the other nine sisters who had died.

To confirm the finding, the team looked at 11 nuns from other convents who had died during the study period. Analysis revealed neurofibrillary tangles in the brains of five of those nuns. Four of the five showed low idea density in their autobiographies.

Among all the nuns with low idea density, the tangles were most striking in the hippocampus and neocortex, the two regions of the brain most affected by Alzheimer's disease.

On the basis of the autobiographies, "we can predict with 90 percent accuracy who is going to get Alzheimer's 60 years later," Snowdon says. "That's pretty potent."

What could account for the differences in the autobiographies? Is the brain already in decline in the young women, or does some inherent characteristic of the brain both contribute to the writing style and put them at risk of Alzheimer's disease?

Typically, sisters with low idea density in their writing relied heavily on lists of

dates and names. "There's nothing wrong with these sentences," says Snowdon. "They're just devoid of ornamentation and ideas."

He believes such sisters suffered from a subtle cognitive glitch—perhaps their memory had already started to malfunction. People who can't remember or store the details of their lives might be forced to recite lists of facts when asked to write an autobiography, he speculates.

"Our findings suggest that Alzheimer's disease may very well be a lifelong process," says coauthor Lydia H. Greiner, also at the University of Kentucky. The damaging brain tangles of the disease may have their genesis decades before the onset of dementia, she speculates. Another study published last year reported similar tangles in the brains of some people who died as young adults, she points out.

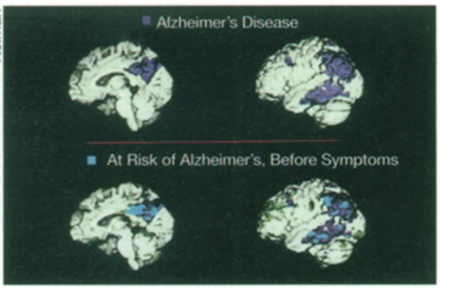
Other scientists don't buy the idea that Alzheimer's disease gets its start very early in life. "I personally don't feel there's enough evidence to suggest that," says Neil Buckholtz of the National Institute on Aging in Bethesda, Md. Many neuroscientists hold that a rich education increases a person's reserve of brain cells or connections between nerve cells, either of which would reduce the risk of dementia, he says.

Although the nun study doesn't support this theory, Snowdon isn't ready to rule it out. This hypothesis holds a great appeal for highly educated researchers. "I hope it's true," Snowdon says.

A more high-tech approach to detecting Alzheimer's disease relies on genetic tests in conjunction with a brain-imaging technique called positron emission tomography (PET). Eric M. Reiman of the Good Samaritan Regional Medical Center in Phoenix and his colleagues knew that people who inherit a gene called *apolipoprotein E-IV* run a 27 percent chance of developing Alzheimer's disease by age 85.

The researchers ran a newspaper advertisement seeking healthy people with a family history of the disorder to participate in a study. They recruited 235 volunteers between the ages of 50 and 65. The researchers then tested the volunteers' blood for the *apo E-IV* gene, located on chromosome 19. They found 11 people who had inherited a copy from each parent. Such people appear to face a 55 percent chance of getting Alzheimer's by age 80. Less than 9 percent of persons with no *apo E-IV* gene have the disease by that age, according to a report in the March NEUROLOGY by Richard H. Myers of Boston University School of Medicine and his colleagues.

The team paired those 11 recruits with 22 controls chosen from their volunteers who had not inherited a copy of the gene. The entire group performed normally on a battery of cognitive tests.



Reiman

*A composite map compares the brain's glucose metabolism in people with Alzheimer's disease, those at risk of this dementia, and controls. The purple areas represent regions of reduced glucose use in Alzheimer's patients only. The blue regions show lowered glucose metabolism in both patients and at-risk individuals. Green represents regions in which glucose use was reduced in the at-risk group only.*

The researchers then used PET to take a closer look at each recruit's brain. These scans can measure the brain's use of the sugar glucose. Reiman's team knew that Alzheimer's disease patients demonstrate less uptake of glucose in certain regions of the brain than people without the disease do. Since nerve cells use glucose to fuel their activities, reduced glucose utilization suggests that some brain cells are damaged or dying.

Using a computer program, Reiman and his colleagues created a map of the brain regions that function abnormally in people with Alzheimer's disease. When they plugged in the data from the recruits, they found that, overall, the group of people who had inherited two *apo E-IV* genes exhibited reduced activity in the same brain regions as Alzheimer's patients.

They also found in those 11 volunteers other brain changes similar to changes observed in people of more advanced age. This finding holds out the tantalizing possibility that the *apo E-IV* gene plays a role in aging, the authors speculate.

This isn't the first time researchers have used PET to look for people at risk of Alzheimer's disease. Last year, a team led by Gary W. Small of the University of California, Los Angeles, School of Medicine also found PET abnormalities in healthy people who had just one copy of the *apo E-IV* gene (SN: 3/25/95, p. 181).

"Our study confirms and extends that important observation," Reiman says.

Together, the new findings hold out the possibility of flagging people at risk of Alzheimer's disease many years before senility sets in. Yet researchers warn that such tests are not yet definitive.

The nun study suggests that young adults' writing samples can reveal people who will become demented later in life, but the test is far from a sure bet. "I think we have to be real careful that we don't scare people into thinking that just because they don't have complex writing, they're going to develop Alzheimer's disease," Buckholtz warns.

By itself, the *apo E-IV* blood test offers no definitive answer on who will develop Alzheimer's disease. The study published in the March NEUROLOGY indicates that many people who have the *apo E-IV* gene never experience the disease's symptoms. It also supports the finding that people with two copies of the gene run the highest risk. Still, statistics can't tell who among such individuals will actually get the disease.

Those uncertainties led a panel convened by the National Institute on Aging and the Chicago-based Alzheimer's Association to advise against using an *apo E-IV* test to calculate future risk. Until further research fills in some of the gaps in knowledge, the genetic test could cause unnecessary anxiety, the group said. They published their report in the April 20 LANCET.

Adding a PET scan to the *apo E-IV* blood test may someday provide doctors with an edge in the fortune-telling department. For now, though, Reiman argues for caution. "At this time, PET scans and *apo E-IV* tests should not be used in healthy individuals to predict their risk of developing Alzheimer's dementia."

The method does offer great promise for the research community. Reiman believes that PET abnormalities become more pronounced as an at-risk individual grows older, and thus successful therapy should stop that progression. If that hunch is confirmed, scientists would be able to use genetic tests along with PET scans to monitor experimental therapy. "We'll have a relatively rapid way to test treatments to prevent Alzheimer's disease," he says.

First, however, scientists must determine whether the combination of PET and blood tests really does forecast dementia, comments Mony J. de Leon, an Alzheimer's researcher at New York University Medical Center. To do this, researchers must continue monitoring their volunteers to see whether they actually develop Alzheimer's, he adds.

This widespread scientific caution may not hold back employers, insurers, and at-risk individuals, however. Snowdon says he has already had calls from insurance companies that want to use the linguistic test to identify people slated for Alzheimer's dementia.

If researchers end up devising a test that reliably foretells a future of dementia, what then? Who should have access to information that may lead to a loss of health insurance or a job? Should doctors offer a predictive test for a disease that has no cure?

Until an effective treatment for Alzheimer's disease is devised, such questions will continue to pose an ethical challenge for society at large. □