

Sister Mary, the gold standard for the Nun Study, was a remarkable woman who had high cognitive test scores before her death at 101 years of age. What is more remarkable is that she maintained this high status despite having abundant neurofibrillary tangles and senile plaques, the classic lesions of Alzheimer's disease. Findings from Sister Mary and all 678 participants in the Nun Study may provide unique clues about the etiology of aging and Alzheimer's disease, exemplify what is possible in old age, and show how the clinical expression of some diseases may be averted.

Key Words: Neuropathology, Alzheimer's disease, Dementia, Cognition

Aging and Alzheimer's Disease: Lessons From the Nun Study¹

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And what was the secret to her longevity? I remember her telling me that one day she had wondered out loud to her doctor if perhaps he was giving her medicine to keep her alive, and after all, her desire was to be with Jesus. Her doctor replied, "Sister, it's not my medicine that's keeping you alive. It's your attitude!" And it was that wonderful attitude that we all loved. It was that attitude that St. Paul describes so well of wanting and not wanting to remain on earth. We all know how much Sister Mary longed for heaven, but we all saw how alert and involved she was in what was going on around her. She was there in the present moment with all her heart and soul. (from Sister Mary's memorial service)

Background

Sister Mary was born in 1892 in Philadelphia, Pennsylvania. In that year Grover Cleveland was elected President of the United States, Toulouse-Lautrec painted "At the Moulin Rouge," and Victoria was still Queen of England. Sister Mary was the first of 11 children of Karl, a German immigrant who worked as a foreman in a hat factory, and Sophie, a Bohemian born in the United States. Both parents were Roman

Catholics, had grade school educations, and were members of the working class.

Shortly before the close of the nineteenth century, Sister Mary began attending St. Boniface Grade School in Philadelphia. A few months shy of her 13th birthday, she received her First Holy Communion. Later that year, her mother died giving birth to Sister Mary's tenth sibling.

Approximately two years later, Sister Mary graduated from the eighth grade. The next month, at age 14, she entered the School Sisters of Notre Dame convent in Baltimore, Maryland. Because of her age, her superiors did not permit her to take her religious vows until five years later. The year she took her vows, her sister Clara entered the Baltimore convent. Thirty years later, Clara died in the holy habit at the age of 49. In 1935, Sister Mary's father died of arteriosclerosis at the age of 68.

At age 19 and with only eight years of formal education, Sister Mary began to teach seventh and eighth grades in schools in the Eastern United States. When she was not teaching, she was attending Holy Angels Academy in Fort Lee, New Jersey. After taking summer courses over a span of 22 years, she was awarded a high school diploma at age 41. Her high school transcript showed that she maintained an 'A' average, with her highest rating of 100 in algebra and her lowest rating of 80 in drawing.

Sister Mary taught full time until she was 77 years old, then worked part time as a math teacher and teacher's aide for several more years. She finally retired at the age of 84, although she once remarked that she had never really retired: "I only retire at night."

Sister Mary spent the last years of her life in the same convent she had entered as a young girl. Although no longer teaching in a schoolroom, she held court in the convent, delivering lessons on aging with grace. Those who met her during those years easily recall the sight and sounds of this remarkable

¹To maintain confidentiality and anonymity, participants in the Nun Study and other epidemiologic studies agree to have their personal data reported in summary or in group reports. We are deeply indebted to Sister Mary for her permission to publish the details of her life and her medical findings in this case report. We also appreciate the spirited support of the members, leaders, and health care providers of the School Sisters of Notre Dame religious congregation. The following people were especially helpful in the present study: Sisters Bernice Feilinger, Louis Marie Koesters, Marlene Manney, Patricia McLaughlin, Marie Kevin Mueller, and Gabriel Mary Spaeth; Ms. Lydia Greiner and Ms. Gari-Anne Patzward; and Dr. William Markesbery. This study was funded by grants from the U.S. National Institute on Aging (R01AG09862, K04AG00553, and 5P50AG05144).

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woman. Sister Mary stood approximately four and a half feet tall, weighed about 85 pounds, and dressed in a full black and white habit. She had a big open-mouthed smile, soft facial skin, and eyes that radiated joy and peace. Her trademarks were a long-beaked green visor she wore to protect her eyes from glare, and a warm and hearty cackle of a laugh that boomed out of her room at all hours of the day and night.

In her "retirement" she continued to be active in her community and concerned about world events. She was an avid reader and was often seen poring over newspapers and books with her magnifying glass. Using a map and a globe, she prayed herself around the world, dedicating a separate day to each continent. She devoted many of her prayers to children and women in need. Because of her concern about the health of younger people, in 1990 she donated her body to the Anatomy Board of Maryland. In letters that she carefully wrote to her family, she described that day as "one of the happiest days of my life."

One year later, she attended a meeting of all the older sisters living in her convent. Sister Mary and her fellow sisters listened intently as scientists from the University of Kentucky described their study on aging and Alzheimer's disease and explained why it was necessary for each participant to donate her brain at death for neuropathologic evaluation. After the presentation, Sister Mary was the first to speak: "Sign me up!"

In so doing, she became one of 678 School Sisters of Notre Dame across the United States to begin participation in the Nun Study. She and all the others agreed to allow investigators full access to their archival and medical records, participate in annual assessments of cognitive and physical function, and donate their brains at death for neuropathologic studies.

All 678 sisters participated in the first functional assessment, and an average of 1.6 years later, 575 survivors participated in a second assessment. At the time of their last assessments, the 678 participants were an average of 85 years of age (range 75 to 102) and 31% of them were cognitively impaired. Sister Mary was 101.1 years old and cognitively intact during her last functional assessment. Eight months later, when she was 101.7 years old, Sister Mary died and became one of the 118 sisters who have donated their brains to the University of Kentucky.

While Sister Mary was alive, she was the gold standard for successful cognitive aging in the Nun Study. After her death, the neuropathologic evaluation revealed a surprising finding: Her brain contained abundant neurofibrillary tangles and senile plaques, the classic neuropathologic lesions of Alzheimer's disease. Although extrapolation of findings from Sister Mary and her fellow sisters may be difficult, the lives of these extraordinary women may provide unique clues to the etiology of aging and Alzheimer's disease, exemplify to others what is possible in old age, and show how the clinical expression of some diseases may be averted.

Cognitive Function

Cognitive function tests used to assess Sister Mary and the other participants in the Nun Study included a battery of neuropsychological tests compiled by the Consortium to Establish a Registry for Alzheimer's Disease (CERAD; Morris et al., 1989), and an additional test, Object Naming, derived from another source (Rosen, Mohs, & Davis, 1984). These eight tests assess memory, concentration, language, visuospatial ability, and orientation to time and place.

At her last functional assessment, Sister Mary received a Mini-Mental State Examination (Folstein, Folstein, & McHugh, 1975) score of 27. This score is well within the normal range of 24 to 30 for that test, which is a well-accepted method of assessing global cognitive function in elderly persons. Sister Mary identified 9 of the 15 line drawings of objects in the Boston Naming test (Kaplan, Goodglass, & Weintraub, 1983), and 8 of the 12 real objects in the Object Naming test. In both tests, she was least likely to make errors identifying objects that were common in everyday usage, such as a bed, and more likely to make errors for objects that were infrequent in everyday usage, such as tongs. When asked to name as many animals as possible in 60 seconds for the Verbal Fluency test (Borkowski, Benton, & Spreen, 1967), she named only 8 animals, 7 of which were named in the first 15 seconds. All of the animals that she named were common, such as dog, cat, and bird. For the Constructional Praxis test, her score of 9 out of a possible 12 indicated that she could draw geometric shapes of moderate complexity.

Sister Mary's ability to learn and remember a list of 10 words was assessed by three tests. In the first test, Word List Memory (Rosen et al., 1984), a list of 10 words is presented three times, and immediately after each presentation the sister is asked to recall the 10 words. Sister Mary's score of 10 out of a possible 30 indicated that she recalled 3 or 4 words after each presentation. Five minutes after the completion of that test, Sister Mary was again asked to recall the list of 10 words. Her score on the Delayed Word Recall test indicated that she could recall 5 of the words. In the third test of memory, Word Recognition, 20 cards are shown to the sister. Printed on these cards are the 10 words from the previous tests, as well as 10 other words. Sister Mary was able to recognize 8 of the words as words that she had been shown previously.

Figure 1 shows how Sister Mary and the other participants in the Nun Study performed on the Mini-Mental State Examination. Her score of 27 on this test was remarkable given that she (a) was 101 years of age when she was examined, (b) had less formal education than 85% of the Nun Study population, and (c) was examined less than a year before her death, which may have diminished her usual test performance because of a "terminal drop" in function that may occur before death. To clarify the possible role of these variables, subsequent analyses compared Sister Mary's cognitive test scores to those

of the other 117 sisters who died (Table 1). The average age at death in these sisters was 88 years (range 77 to 103).

For seven of the cognitive tests, Sister Mary's performance was equal to or slightly higher than the average observed in the other sisters who died. For the eighth test, the Mini-Mental State Examination, her score was 10 points higher than the average score of the other 117 sisters. However, when Sister Mary's old age and low education were considered in a regression analysis, she did substantially better on each of the eight tests than did the other sisters (Table 1). For example, Sister Mary's score of 27 on the Mini-Mental State Examination was well above the 4 that was predicted based on her old age and low education. Much of Sister Mary's deviation from the predicted score was due to her old age, rather than to her low education. Her predicted Mini-Mental State Examination score was 8 based on her old age alone, compared with 11 based on her low education alone.

Other analyses also indicated that during the year before her death, Sister Mary experienced less change in her cognitive function test scores than did other sisters who died. A total of 37 of the 118 sisters who died survived long enough to participate in the second annual functional assessment. The average age of these 37 sisters (at the midpoint between the first and second examinations) was 86 years (range 76 to 100). Although the average sister showed a 1- to 3-point annual decline in test scores, Sister Mary had a 1- to 2-point increase in Mini-Mental State Examination, Delayed Word Recall, and Verbal Fluency scores; no change in Word Recognition and Constructional Praxis scores; and a 1- to 2-point decrease in Word List Memory, Boston Naming, and Object Naming scores.

Informal interviews with her health care providers also were conducted in order to arrive at a better understanding of her cognitive function during the 10 years before her death. According to these interviews, Sister Mary's cognitive function was stable

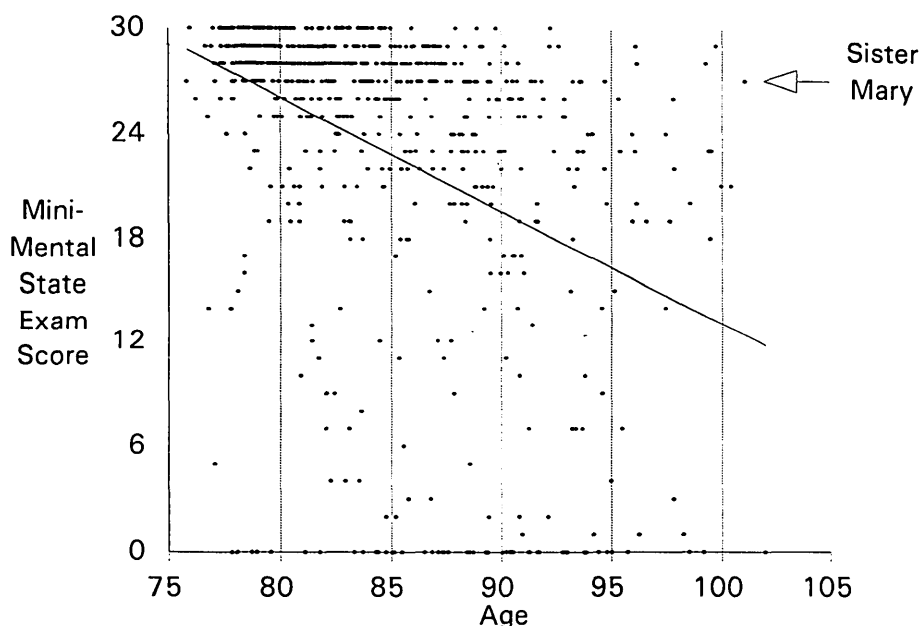


Figure 1. Age and Mini-Mental State Exam Score and best fit regression line in 678 participants in the Nun Study.

Table 1. Cognitive Function Test Scores for Sister Mary and the Other Sisters Who Died in the Nun Study

	Cognitive test							
	Mini-Mental State Exam	Boston Naming	Object Naming	Verbal Fluency	Word List Memory	Delayed Word Recall	Word Recognition	Constructional Praxis
Sister Mary's actual score	27	9	8	8	10	5	8	9
Unadjusted mean in other sisters	17	7	7	8	10	3	5	6
Sister Mary's predicted score based on the other sisters	4	2	2	1	0	0	1	2
P-value for difference between actual and predicted score	0.01	0.05	0.05	0.09	0.09	0.03	0.02	0.02

Note: Predicted scores were adjusted for days between the exam and death, age at time of the exam, and attained education. P-value was based on the Student test, and was a test of the hypothesis that Sister Mary's scores were higher than those predicted based on the scores of the 117 other sisters who died.

and did not visibly change during most of the 10 years. However, it was affectionately reported that a couple of years before her death she had stopped "bossing the other sisters around," and that a few weeks before her death she had become quieter and less energetic. Standard nursing reports taken during the week preceding her death indicated that Sister Mary had no difficulty remembering a short list of items, grasping situations and explanations, and recalling recent events. Sisters who were with her at the time of her death indicated that her mind was clear until the end.

Medical History

Reliable information on Sister Mary's medical history was available for the last decade of her life. Her cause of death was listed as metastatic adenocarcinoma of the colon, although she had other health problems that may have contributed to her death. She had polymyalgia rheumatica, calcium pyrophosphate deposition disease, Stokes-Adams Syndrome, and chronic anemia. Sister Mary also had episodes of supraventricular tachycardia with syncope. An electrocardiogram taken 16 months before her death showed atrial fibrillation, marked S-T depression consistent with subendocardial injury, and atrioventricular block. A few months before her death she weighed approximately 70 pounds. Standard weight measurements taken as part of the Nun Study indicated that she had lost approximately one-half of a pound per month during the last two years of her life.

Some of these conditions should have, or may have, reduced Sister Mary's cognitive function, because the presence of heart disease and other chronic diseases may be associated with diminished cognitive function. Preliminary findings from the Nun Study also indicate that very low body weight and significant weight loss have moderately strong associations with poor performance on the cognitive function tests.

Neuropathologic Evaluation

At death, Sister Mary and all participants in the Nun Study donate their brains to the University of Kentucky for gross and microscopic studies. The major emphasis of these studies is on the neuropathology of Alzheimer's disease.

The classic lesions of Alzheimer's disease, neurofibrillary tangles and senile plaques, are counted in the hippocampus (CA1 and subiculum regions) and neocortex (frontal, temporal, parietal, and occipital lobes). Bielschowsky stained sections of the brain are used to count the number of senile plaques per low power field ($10\times$) in the 10 most involved 2.35 mm^2 fields, and the number of neurofibrillary tangles per moderate power field ($20\times$) in the 10 most involved $.586\text{ mm}^2$ fields. Senile plaques are differentiated into neuritic and diffuse plaques, and lesion counts are summed across the two regions of the hippocampus and the four lobes of the cerebral cortex. Brain infarctions visible to the eye also are identified.

Neuropathologic evaluations have been completed on 118 sisters. Findings from the neuropathologic evaluations for Sister Mary and the other sisters are presented in Table 2. Compared with the averages for the other sisters who died, Sister Mary had fewer neurofibrillary tangles and neuritic plaques in the neocortex; more neurofibrillary tangles, neuritic plaques, and diffuse plaques in the hippocampus; and more diffuse plaques in the neocortex. Only one other sister had higher counts of diffuse plaques in the hippocampus and neocortex than did Sister Mary.

Sister Mary's brain weighed 870 grams at death. Only five other sisters had brains that weighed less. Sister Mary's low brain weight may have been a consequence of her extensive Alzheimer's disease neuropathology and/or her small stature. Her neuropathologic evaluation indicated a moderate degree of frontal, parietal, and temporal lobe atrophy.

There were no infarcts in Sister Mary's brain, despite the fact that lacunar and larger infarcts were present in 71% of the sisters who were 95 years of age or older at death. Sister Mary did show focal atherosclerotic deposits in the middle cerebral, internal carotid, and vertebral arteries.

Neuropathology and Cognitive Function

Neuropathologic and neuropsychological findings from the Nun Study shed some light on how Sister Mary may have maintained a relatively high level of cognitive function at such an old age. Preliminary

Table 2. Alzheimer's Disease Lesion Counts and Brain Weight in Sister Mary and the Other Sisters Who Died in the Nun Study

	Neurofibrillary Tangles in Neocortex	Neurofibrillary Tangles in Hippocampus	Neuritic Plaques in Neocortex	Neuritic Plaques in Hippocampus	Diffuse Plaques in Neocortex	Diffuse Plaques in Hippocampus	Brain Weight in Grams
Sister Mary's actual value	1	57	3	6	179	32	870
Unadjusted mean in other sisters	11	20	15	3	92	7	1120
Sister Mary's predicted value based on the other sisters	14	22	10	1	55	4	1007
P-value for difference between actual and predicted values	0.59	0.14	0.60	0.42	0.02	0.001	0.24

Note: Predicted values were adjusted for age at death and attained education. P-value was based on the Student test, and was a test of the hypothesis that Sister Mary's values were different from those predicted based on the values of the other sisters who died. Means were based on 110 to 116 sisters (since lesion counts were not possible in some sisters because a brain infarction had obliterated a specific brain region, and brain weight was unavailable for one sister).

findings on the 118 sisters who died indicate that neurofibrillary tangles in the neocortex have strong associations with poor performance on each of the eight cognitive function tests, whereas neurofibrillary tangles in the hippocampus have moderately strong associations with poor performance on tests of memory. Sisters with brain infarcts or with brain weights of less than 1,000 grams also showed significantly lower performance on the cognitive tests than did sisters without these conditions. Although neuritic plaques in the hippocampus and neocortex were associated with poor performance on the cognitive tests, these associations were dramatically reduced in strength after adjustment for the number of neurofibrillary tangles. Diffuse plaques in the hippocampus and neocortex had weak and inconsistent associations with performance on the eight cognitive tests.

Given these relationships, Sister Mary may have maintained relatively high cognitive function during old age because of the type and location of her Alzheimer's disease lesions and the absence of brain infarcts. Although she had a relatively high number of neurofibrillary tangles in her brain, very few were present in the neocortex. Lack of significant numbers of these lesions in the association areas of the neocortex may have spared her from significant deterioration in performance on tests of language, orientation to time and place, and visuospatial ability. Her exceptionally high numbers of diffuse plaques in the hippocampus and neocortex also may have reflected a less severe form of Alzheimer's disease. Lack of a brain infarct also may have spared Sister Mary from significant loss of cognitive function and eliminated the possibility that infarcts increased the cognitive effects of the neuropathologic lesions of Alzheimer's disease. Her low brain weight, however, suggests that she was not buffered against the cognitive effects of her neuropathologic lesions because of a large volume of reserve brain tissue.

Neuropathologic Criteria for Alzheimer's Disease

In 1907, Alois Alzheimer published the first case study of what is now known as Alzheimer's disease. As indicated by the title of that case report, "About a Peculiar Disease of the Cerebral Cortex," Dr. Alzheimer suggested that the patient's intellectual and social declines were related to "a tangled bundle of fibrils" [neurofibrillary tangles] in the neocortex; however, he also observed "mileary foci [senile plaques] . . . scattered over the entire cortex" (Alzheimer, 1987). Since the publication of that case study, a debate has raged over the importance of neurofibrillary tangles and senile plaques in Alzheimer's disease. During the last 10 years, the debate has expanded to include discussions of the significance of neuritic and diffuse plaques, the two types of plaque that make up senile plaques.

Nearly 90 years after the first description of Alzheimer's disease, it is still not clear which neuropathologic lesions are more closely related to the onset and progression of the symptoms of Alzheimer's

disease. This uncertainty is due in part to the presence of Alzheimer's disease lesions in subjects who do not exhibit the symptoms of the disease (Crystal et al., 1988). Furthermore, several studies have suggested that the development of senile plaques and neurofibrillary tangles may be an inevitable consequence of aging (Crystal et al., 1988; Giannakopoulos et al., 1995; Stam, Wigboldus, & Smeulders, 1986). This possibility has made it difficult for neuropathologists to discriminate the pattern of neuropathologic lesions that occurs with Alzheimer's disease from the pattern of lesions that may occur with normal aging.

Two neuropathologic criteria are currently widely used in the diagnosis of Alzheimer's disease. In the first criterion, commonly referred to as the Khachaturian criterion, the neuropathologic determination of Alzheimer's disease in elderly persons is based on the number of neocortical senile plaques (Khachaturian, 1985). In the second criterion, commonly referred to as the CERAD criterion, the neuropathologic determination of Alzheimer's disease is based on the number of neocortical neuritic plaques (Mirra et al., 1991). Recent studies, however, indicate that neocortical neurofibrillary tangles should also be considered in neuropathologic criteria for Alzheimer's disease (Bierer et al., 1995; Bouras, Hof, Giannakopoulos, Michel, & Morrison, 1994; Nagy et al., 1995).

Unfortunately, the validity of different neuropathologic criteria for Alzheimer's disease has rarely been tested. This deficiency is largely due to the general lack of availability of nondemented (control) brains for scientific studies. In one of the few studies that attempted to validate a neuropathologic criterion for Alzheimer's disease, 142 demented brains were compared to only 8 nondemented brains, and the demented patients were an average of 11 years older than the nondemented patients (Mirra et al., 1991).

The Nun Study is unique in that it includes a large number of brains from people who are not demented. Preliminary findings from the Nun Study indicate that the Khachaturian (senile plaque) criterion has a relatively high ability to discriminate demented from nondemented individuals. The CERAD (neuritic plaque) criterion, however, has a relatively moderate ability to discriminate demented from nondemented individuals. Sister Mary had enough neocortical senile plaques to meet the Khachaturian criterion for Alzheimer's disease, but not enough neocortical neuritic plaques to meet the CERAD criterion for Alzheimer's disease.

One of the most distinguishing neuropathologic features of Sister Mary's brain was the abundance of neocortical diffuse plaques (Table 2). Approximately 86% of the participants in the Nun Study had neocortical senile plaques and among the members of this subgroup, neocortical diffuse plaques made up 84% of those senile plaques (range 25% to 100%). Findings from the Nun Study indicate that neocortical diffuse plaques have a stronger negative association with brain weight than do either neocortical neurofi-

brilliant tangles or neuritic plaques. The age- and education-adjusted Spearman rank correlation between neocortical diffuse plaques and brain weight was $-.32$ (p -value $< .001$). These preliminary findings suggest that neocortical diffuse plaques may play a role in the brain atrophy that is present in many Alzheimer's disease patients. Out of the first 118 deaths in the Nun Study, Sister Mary had the second highest neocortical diffuse plaque count and the sixth lowest brain weight.

Alzheimer's disease is probably a heterogeneous disease process with a variety of constellations of neuropathologic features and clinical outcomes. Although it is arguable whether Sister Mary had the type and quantity of neuropathologic lesions that are necessary to meet the neuropathologic criteria for Alzheimer's disease, her neuropathologic lesions still may have caused damage to her brain and reduced her cognitive abilities, although not enough to qualify for a clinical diagnosis of dementia. Although the abundant neurofibrillary tangles in her hippocampus may have affected her memory, the abundant diffuse plaques in her neocortex also may have contributed to the atrophy of her neocortex and the low weight of her brain.

Cognitive Impairment Is Not an Inevitable Consequence of Aging and Disease

Sister Mary taught thousands of students in classrooms during a career that spanned nearly seven decades. When she retired from the classroom at age 84, she continued her mission as an educator until her death 17 years later. During the last decades of her life she taught her fellow sisters, her grandnieces and grandnephews, and her doctors and nurses that it was possible to age with grace, joy, and beauty. Because of her participation in the Nun Study, her lessons on aging and Alzheimer's disease can be shared with others.

Although Sister Mary was not the first to live to very old age with intact cognitive function, she may have been the first on record to do so in the presence of such abundant Alzheimer's disease lesions. Compared with other sisters who died, she had relatively high counts of neurofibrillary tangles and senile plaques. Sister Mary also had many health problems, from cancer to heart disease, and had progressively lost weight during the last few years of her life. Such weight loss, numerous chronic diseases, and abundant Alzheimer's disease lesions would be expected to affect the cognition of most people. Sister Mary, however, appeared to be cognitively intact, with good short-term memory and excellent orientation to her surroundings and current events, in spite of being an apparently frail centenarian.

Sister Mary may have entered old age with superior cognitive ability and, as the neuropathology of Alzheimer's disease spread in her brain, slipped from a superior to a very good level of cognitive performance, without dropping to a functional level typical of someone with dementia. Alternatively, the type and location of the lesions of Alzheimer's dis-

ease in her brain may have represented a less severe form of the disease process. Most notable was the small number of neurofibrillary tangles in her neocortex. Of all the neuropathologic lesions of Alzheimer's disease investigated in the Nun Study, neocortical neurofibrillary tangles had the strongest associations with the clinical diagnosis of dementia and poor performance on each of the eight tests of cognitive function. Lack of brain infarcts and other neuropathologic diseases also may have protected her from the loss of cognitive function normally expected in someone of her age.

Alzheimer's disease is probably not a disease that is simply present or absent. It is likely to be a disease with a wide range of clinical manifestations, from subtle to severe. In the future we will add other neuropsychological tests to the Nun Study to evaluate higher levels of cognitive performance than is possible with the present battery of tests. The resulting data should help us to determine if Alzheimer's disease lesions are associated with declines in cognitive function that may, nonetheless, leave persons with test scores that fall within the normal range. Furthermore, we will investigate whether the lesions of Alzheimer's disease have a more potent relationship to cognitive function loss in persons who are compromised by the presence of other neuropathologic diseases and low brain reserve (e.g., a low number of functional neurons).

Advances Come From the Sacrifices of Ordinary and Exceptional People

Knowledge concerning the causes and prevention of chronic diseases has come largely from epidemiologic studies in which the life histories of people with disease are compared to life histories of those without disease. Genetic, lifestyle, and environmental factors that are more prevalent in those with the disease (than in those without the disease) are identified as risk factors.

Little progress has been made, however, in understanding how lifestyle and environmental factors relate to the development of Alzheimer's disease. This is largely due to the disease itself. Memory impairments associated with Alzheimer's disease prevent those with the disease from telling us their histories. (The existence of convent archives makes this less of a problem in the Nun Study.) Furthermore, the past histories of those without the disease are difficult to ascertain because of the reluctance of many normal healthy people to participate in Alzheimer's disease research and, in particular, to donate their brains at death for neuropathologic studies.

To gather accurate data on past exposures to potential risk factors, more longitudinal population-based studies of Alzheimer's disease must be conducted. Participants in such studies should initially be cognitively intact so that reliable historic data can be collected concerning their past exposures (e.g., head trauma, smoking, and medications). Furthermore, the cognitive abilities of such participants need to be documented before they exhibit the clini-

cal symptoms of dementia. Such baseline cognitive data is necessary if we are ever to determine the full extent of the cognitive dysfunction caused by Alzheimer's disease.

Although longitudinal studies are expensive and difficult to fund, a greater problem is the recruitment of normal healthy elderly people to participate. Participants in these studies must make great personal sacrifices. They must tell investigators considerable details about their lives. They must regularly undergo extensive neuropsychological testing which may prove embarrassing if they begin to experience age-associated declines in function. And if we are to make any real progress in disentangling the causes of brain diseases, participants must donate their brains at death.

We need more people like Sister Mary who are willing to make such sacrifices. Sister Mary did not directly benefit from participation in the Nun Study, but her friends and family knew that she felt better for doing it. She was willing to lay out her life, her cognitive function, and her brain in all their details. Her only request was that we simply refer to her as Sister Mary. She did not want to become a celebrity. She did not want the accolades. She only wanted to help younger people who would one day reach old age. Surely there are many others who are willing to leave such a legacy.

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