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*Modern Concepts in*

# Alzheimer's Disease

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Editors

Daniel E. Wexler, Ph.D.

Kristi A. Potochnik

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Editor's Note:

The 1998 edition of 'Modern Concepts in Alzheimer's Disease' contains reprints that in our judgement are the most cogent and useful articles written by scientists for the scientific and medical communities. These articles were chosen for relevance, detail of content, usefulness in a clinical context, and readability. In preparing this volume, we culled literally thousands of titles to glean those most understandable and useful to health professionals. In addition, we have included a highly insightful thesis by Dr. Marie Therese Duncan on the transition process from home care to formal care.

This edition is intended to serve the health professional as an up-to-date and comprehensive handbook of information on Alzheimer's disease. It should certainly also be useful to educated consumers who wish to have accurate and in-depth information on the disease for personal guidance on the road ahead.

-Daniel E. Wexler, Ph.D.

-Kristi Potochnik

# Alzheimer's Disease

# Forward

DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health Statement of Richard J. Hodes, M.D.

Director, National Institute on Aging Hearing of the U.S. Senate Labor and Human Resources Committee Subcommittee on Aging

## **"Meeting the Challenges of Alzheimer's Disease: The Biomedical Research That Will Carry Us into the 21st Century" June 5, 1997**

Chairman Gregg and Members of the Senate Labor and Human Resources Subcommittee on Aging, we are engaged in a remarkable period of Alzheimer's disease discovery. Not long ago, "senility" was thought to be an inevitable consequence of aging, but research has since proved that, without disease, the human brain continues to function well throughout life.

Dementia, or the loss of intellectual function, results from disease, and Alzheimer's disease is the most common cause of dementia in older people. Tragically, an estimated four million people now suffer from Alzheimer's disease, a progressive brain disorder marked by an irreversible decline in intellectual abilities and by changes in behavior and personality. Alzheimer's disease devastates its victims. Although the early signs involve mild forgetfulness, the dementia ultimately leaves patients incapable of caring for themselves. Behavior changes may cause patients to become agitated, sometimes to the point of causing harm to themselves or others. As a result, Alzheimer's disease has a profound effect on the millions of family members and other loved ones who provide most of the care for people with this disease.

Because the prevalence of Alzheimer's disease doubles every five years beyond age 65, the rapid growth of the oldest old population is expected to place a significantly greater number of people at risk for the disease. Some scientists have projected a tripling of Alzheimer's disease patients by the year 2050 to 14 million individuals. It is urgent that we define the causes and features of Alzheimer's disease and find ways to combat it.

Fortunately, as understanding of the disease grows, so do the opportunities for developing interventions to halt or slow its progress. The National Institute on Aging (NIA) leads a national effort, in collaboration with several components of the National Institutes of Health and other agencies, to conquer this devastating disease by working to understand the biological mechanisms underlying Alzheimer's disease, to develop treatments and cures based on research findings, and eventually to discover ways to prevent the disease.

Pathological signs. When Dr. Alois Alzheimer studied the pathology of this dementia in 1907, he described two distinctive features in the brain that still characterize the disease. The first feature is the plaque, composed largely of a protein fragment called beta-amyloid, normally secreted by brain cells. Plaques gradually accumulate in the spaces between nerve cells in the brains of patients with Alzheimer's disease. Many scientists believe that beta-amyloid contributes to the nerve cell death that leads to dementia in Alzheimer's disease.

The other feature is the neurofibrillary tangle, which is composed mainly of an abnormal form of

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a protein called tau. Normally, tau supports the microtubular structure that transports molecules within nerve cells. In Alzheimer's disease, however, abnormal tau accumulates to form tangles inside nerve cells, disrupting cell functions. Scientists also believe that tangles could cause cell injury and death as they build up inside cells.

While some plaques and tangles occur with normal aging, they are much more numerous in persons with Alzheimer's disease. A significant amount of research is devoted to understanding the origin of plaques and tangles in Alzheimer's disease and to learning how they relate to nerve cell death, loss of neuronal connections, and other features, such as inflammation, also seen in the brains of Alzheimer's disease patients. Scientists hope to translate this knowledge into therapies that will slow or prevent the progress of Alzheimer's disease.

For many decades after Dr. Alzheimer described plaques and tangles, these features were not commonly associated with the dementia of old age, which was widely believed to be an 'inevitable consequence of aging. This belief has largely been dispelled by a broad scientific initiative to understand the disease. Researchers have recognized different forms of Alzheimer's disease. In some individuals, symptoms occur in persons as young as 30 years. This rare, early-onset form of Alzheimer's disease occurs in a small number of individuals and accounts for approximately 10 percent of cases of Alzheimer's disease. The common, late-onset form of Alzheimer's disease, in which symptoms appear after age 65, accounts for approximately 90 percent of cases.

Genetic links. Beginning in 1990, research has produced a remarkable series of genetic discoveries. Researchers identified mutations in three genes that cause the familial, early-onset form of the disease, and identified a fourth gene that is a risk factor for the common, late-onset form of the disease. The first early-onset gene mutation discovered, on chromosome 21, is in the gene that codes for the parent protein of the beta-amyloid peptide found in plaques. Mutations were soon found in genes on chromosomes 14 and 1, associated with early-onset Alzheimer's disease. Mutations in the chromosome 14 gene are the most common, being responsible for 40 to 50 percent of early-onset cases inherited in families. In these early onset cases, inheritance of just one copy of the mutated gene causes the disease. In addition, there remain some familial, early-onset Alzheimer's disease cases not caused by mutations in any of the known genes, making it likely that there are more genes still to be identified.

The fourth gene, associated with the more common form of Alzheimer's disease in which symptoms occur in later years, was found on chromosome 19. Knowing that there were families in which many members developed Alzheimer's disease late in life, researchers looked for a genetic link. The search led to a gene that codes for forms (alleles) of the protein apolipoprotein E (ApoE). One of the forms, ApoE4, is now recognized as the first genetic risk factor identified for the common, late-onset form of Alzheimer's disease. Epistemological studies have suggested that the age of onset of Alzheimer's disease can vary by as much as 20 years depending on whether a person inherits no copies, one copy, or two copies of ApoE4. Recent research findings support the possibility that development of at least some cases of late-onset Alzheimer's disease involves other risk factor genes, and investigators are pursuing the location of these genes on other chromosomes, as well as their identification.

To aid in analyzing the disease process in the different forms of Alzheimer's disease, researchers last year genetically engineered a transgenic mouse. The mouse carries mutated human genes associated

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with Alzheimer's disease. This is the first animal model to exhibit some of the cognitive as well as the neuropathological features of Alzheimer's disease. This model provides an important research tool for understanding Alzheimer's disease and for expediting the testing of potential Alzheimer's disease drug therapies.

Ethical issues. A degenerative disease such as Alzheimer's disease raises important ethical questions regarding care, genetic testing, and research. Considerable attention has been given to the ethics of elective genetic testing for Alzheimer's disease, apart from research purposes. Predictive testing is possible in the autosomal dominant genes linked to early-onset families. The ApoE allele, however, is not absolutely predictive of Alzheimer's disease in asymptomatic individuals. To date, there is a consensus among most researchers, policy experts, ethicists, and others, that except for autosomal dominant early-onset families, Alzheimer's disease genetic testing should not be used for screening or diagnosis in asymptomatic individuals. Genetic testing is currently a particular concern given the potential for employment and insurance discrimination.

Issues of informed consent, both for health care and for participation in research, are of particular concern for Alzheimer's disease patients and others with diminished cognitive abilities. Special efforts are being made to improve the consent process for care, to encourage advance care planning while the patient is able, and to make the consent process meaningful to potential participants in Alzheimer's disease intervention studies.

Potential for early detection. The genetic involvement of Alzheimer's disease offers a number of opportunities for discovering disease mechanisms, improving diagnostic tests, and identifying targets for treatment. For example, scientists recently studied the cognitive and brain function of volunteers aged 50 to 64 years to compare those having two copies of the ApoE4 allele (who are at high risk for developing Alzheimer disease) with controls having no ApoE4 allele. Although neuropsychological tests found all volunteers to be cognitively normal, brain imaging technology showed that an increased proportion of individuals with two ApoE4 alleles had reduced glucose metabolism in the same areas of the brain as patients with probable Alzheimer's disease. These findings indicate that it may be possible to identify brain function abnormalities in persons with no clinical symptoms who are at high risk for Alzheimer's disease many years before they would be expected to develop such symptoms. This provides opportunities for the development of early interventions that would delay or prevent the brain damage seen in fully developed Alzheimer's disease. Stopping or delaying the progression of the disease prior to onset of noticeable symptoms would make a major contribution to quality of life and continued function.

Early recognition and appropriate assessment of Alzheimer's disease are critical goals. Family members, especially spouses, can be instrumental in interpreting early signs and symptoms and seeking evaluation and treatment. A study of Japanese-American men and their families in Hawaii, however, found that many wives and other family members had not recognized or reported memory problems in individuals with mild to more severe dementia. Further, more than half of the individuals with recognized memory problems had not received a dementia evaluation. These results highlight the importance of public education efforts to improve recognition and reporting of symptoms very early in the illness in order to take advantage of interventions for individuals with potentially treatable dementias, and to help patients and families plan for the future.

Epidemiologic research. While determining the prevalence of Alzheimer's disease in the United

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States is important for health policy formulation and research planning, differing Alzheimer's disease prevalence estimates generated by studies in various populations provide key evidence suggesting potential risk factors (both genetic and environmental) as well as protective factors. Epidemiologic studies, particularly those comparing different populations, provide crucial clues to these factors, as well as to the causes of and potential treatments for Alzheimer's disease. Triggered by clues from basic research, epidemiologic studies have been very effective, for example, in helping to identify genetic and environmental risk and protective factors for Alzheimer's disease. As a result of epidemiologic research, age, a history of severe head trauma, and coexisting medical conditions, such as vascular disease, are now viewed as potential Alzheimer's disease risk factors. In contrast, high levels of education and cognitive ability have been linked to lower risk for developing Alzheimer's disease in late life.

Epidemiologic studies have also suggested that estrogen replacement therapy, use of non-steroidal anti-inflammatory drugs, and use of anti-oxidants are protective against Alzheimer's disease. One such study provided the strongest evidence to date that taking estrogen after menopause may delay the onset and reduce the risk of Alzheimer's disease in postmenopausal women. In this study, 16.3 percent of the women who had not used estrogen developed Alzheimer's disease, while only 5.8 percent of the women who had taken estrogen developed the disorder. Recent results of a 15-year study found that anti-inflammatory drugs such as ibuprofen, taken for as little as two years, also appear to reduce the risk of Alzheimer's disease. In most forms of Alzheimer's disease, therefore, disease progress may be influenced by multiple factors.

Coexisting vascular disease. We are also learning more about the relationship of AD to other conditions affecting older persons. In a recent finding that described the coexistence of Alzheimer's disease with vascular disease in elderly U.S. nuns, the presence of small strokes in parts of the brain below the cortex resulted in more severe dementia than expected on the basis of Alzheimer's disease neuropathology alone. In comparison, people with such small strokes in any brain region in the absence of Alzheimer's disease neuropathology generally had no significant changes in cognitive function when compared with controls. Approximately half of the demented patients 'in this autopsy study had these small strokes. These results strongly suggest that prevention or treatment of vascular disease could delay or reduce the development of symptoms in many Alzheimer's disease patients.

Clinical studies. In order to speed the discovery, development, and testing of new compounds to treat Alzheimer's disease, the NIA complements its broad basic research efforts with strategies that encourage the translation of basic research findings to the development of interventions to be tested in clinical studies. NM's Drug Discovery Groups represent an innovative approach to fostering this process. These research teams are expanding the range of pharmacologic and behavioral approaches to the treatment of Alzheimer's disease and exploring the development of novel delivery systems to the brain.

NIA's Alzheimer's Disease Cooperative Study (ADCS) coordinates the efforts of 35 institutions to rapidly respond to ideas for potential treatments by conducting clinical studies for the treatment of cognitive impairment and behavioral disorders associated with Alzheimer's disease. The design of this consortium makes it possible to conduct multiple clinical studies simultaneously in response to rapidly-emerging scientific opportunities. Evidence from basic and epidemiologic research has

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stimulated clinical studies of anti-oxidants, anti-oxidant inflammatory agents, and estrogen to explore ways of slowing the degenerative progress of Alzheimer's disease. A recently completed clinical trial, conducted by the ADCS, assessed the effectiveness of selegiline (an anti-oxidant drug used in Parkinson's disease) and vitamin E (an anti-oxidant vitamin), both separately and in combination, in delaying the progression of Alzheimer's disease. This trial showed that selegiline and vitamin E may slow development of functional signs and symptoms of Alzheimer's disease by about seven months. Each of the two drugs delayed important milestones for people with moderately severe Alzheimer's disease, such as entry into nursing homes and loss of ability to perform activities of daily living. Delays in the onset of ever more troubling symptoms are viewed by caregivers as an important step.

The ADCS is now studying the effects of other promising therapies, including the steroidal anti-inflammatory agent prednisone; the efficacy of estrogen replacement therapy in women with mild to moderate Alzheimer's disease; and the impact of psychoactive drugs and behavior management techniques to reduce disruptive, agitated behavior in Alzheimer's disease patients.

In addition, a large NIH randomized trial of hormonal replacement, the Women's Health Initiative, is being used to test the ability of hormonal replacement to prevent cognitive decline.

Caregiving. The prolonged and intense caregiving of Alzheimer's disease patients affects the physical, mental, and social health of the caregiver. Fatigue, insomnia, and other physical symptoms are frequent. Depression is not uncommon. Cardiovascular risk factors, such as high blood pressure, may be affected. In response, scientists are testing various methods to help family members who care for people with Alzheimer's disease. Strategies are being developed to increase the caregiver's emotional support, improve services that ease the burden for caregivers, and provide knowledge and skills training useful for coping with the symptoms of Alzheimer's disease.

Families find decisions surrounding placement in a nursing home extremely difficult. Research is helping to define whether and when to turn to a nursing home, and to evaluate what type of care is best for the patient. Additional studies are identifying the strategies that promote the most effective, highest quality institutional care.

Future research. Alzheimer's disease is a devastating condition that ruins the lives of those who have the disease and disrupts the lives of their caregivers. Over the last five years, research has resulted in major advances in our understanding of the disease, including the discovery of genetic components, detection of risk factors, and identification of potential protective interventions. As the pace of research accelerates, new findings will make possible better understanding of factors contributing to nerve cell death and will improve our ability to predict who is at risk for developing Alzheimer's disease. We are at the threshold of further discoveries that will lead to more accurate methods of diagnosis, and to the development of more effective treatments and preventive interventions to reduce the scourge of Alzheimer's disease.

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# Alzheimer's Disease Statistics Fact Sheet

*Alzheimer's disease (AD) is a progressive, degenerative disease of the brain, and the most common form of dementia. Some things you should know about Alzheimer's disease:*

- Approximately 4 million Americans have AD. In a 1993 national survey 19 million Americans say they have a family member with AD, and 37 million know someone with AD.
- 14 million Americans will have AD by the middle of the next century unless a cure or prevention is found.
- One in 10 persons over 65 and nearly half of those over 85 have AD, a small percentage of people in their 40s and 50s get the disease.
- A person with AD will live an average of 8 years and as many as 20 years or more from the onset of symptoms.
- U.S. society, spends at least \$100 billion a year in AD. Neither Medicare nor private health insurance covers the long term type of care most patients need.
- More than seven of ten people with Alzheimer's disease live at home. Almost 75% of the home care is provided by family and friends. The remainder is "paid" care costing an average of \$12,500 per year. Families pay almost all of that out-of-pocket.
- Half of all nursing home patients suffer from AD or a related disorder. The average cost for a patient's care in a nursing home is \$42,000 per year, but can exceed \$70,000 per year in some areas of the country.
- The average lifetime cost per patient is \$174,000.
- Alzheimer's disease is the third most expensive disease in the United States, after heart disease and cancer.
- The federal government will spend approximately \$309 million for Alzheimer disease research in 1996. This represents \$1 for every \$324 the disease now costs society. The federal investment in heart disease, cancer, and AIDS is four to seven times higher.

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The Alzheimer's Association is the only national voluntary health organization dedicated to research for the causes, cures, treatments and prevention of Alzheimer's disease and to providing education and support services to Alzheimer patients, their families and caregivers.

For further information on statistics, please contact the Benjamin B. Green-Field Library at the Alzheimer's Association at 312-335-9602.

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## **Part 1**

# **Overview: Unraveling the Mystery**

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# Alzheimer's Disease: Unraveling the Mystery

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## Preface

Over the past few decades, Alzheimer's disease has emerged from obscurity. Once considered a rare disorder, it is now recognized as a major public health problem having a severe impact on millions of Americans and their families. Research on Alzheimer's disease has grown accordingly. The small group of pioneers who conducted research on the disease in the 1970's has expanded to thousands of scientists in laboratories, institutions, and communities all over the world.

At the National Institutes of Health (NIH), several institutes conduct and sponsor studies on Alzheimer's disease, including the National Institute of Neurological Disorders and Stroke, the National Institute of Mental Health, and the National Institute of Nursing Research. The lead agency for Alzheimer's research at NIH is the National Institute on Aging (NIA), which launched an Alzheimer's disease program in 1978. Since then the study of this disease has become one of NIA's major priorities.

In the private sector, the Alzheimer's Association and other groups are working to combat this disease. They fund research, contribute to public policy decisions, inform and educate the public, and provide services to people with Alzheimer's disease and their families. Their support for research is critical in the effort to understand and defeat this disorder.

Thanks to these many groups, the study of Alzheimer's disease is moving ahead rapidly. Based on the pace of research over the past two decades, many scientists now think that effective treatments

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are not far in the future. The purpose of this booklet is to describe what we have learned to date and where research is now headed in the search for answers about Alzheimer's disease.

About using this booklet

This booklet was written for people who are interested in research on Alzheimer's disease. Technical terms, if italicized in the text, are defined in a glossary. The booklet covers numerous areas of research briefly; for those who want to pursue a specific topic, each chapter ends with a list of review articles and other materials that provide more detail on the studies mentioned in the text. More information on Alzheimer's disease research is also available from the publications and organizations listed at the end of the booklet.

Many people contributed to this booklet. The NIA extends special thanks to the managers and residents of Sunrise of Arlington for the photographs by Richard Nowitz; and to researchers in NIA's Laboratory of Neuroscience for the photographs by Kay Chernush.

This booklet was written by Caroline McNeil, Public Information Office, NIA; designed by Beth Singer Design; and illustrated by Lydia Kibiuk.

# What Is Alzheimer's Disease?

"With Alzheimer's people, there's no such thing as having a day which is like another day. Every day is separate....it's as if every day you have never seen anything before like what you're seeing right now." -- Cary Henderson

This excerpt from the journal of a man with Alzheimer's disease offers a glimpse of what it's like to be one of the 4,000,000 people in the United States who have this progressive, degenerative brain disorder. Cary Henderson, a history professor in Virginia, was diagnosed with Alzheimer's disease at age 55.

Alzheimer's disease is one of the most common causes of the loss of mental function known broadly as dementia. This type of dementia proceeds in stages, gradually destroying memory, reason, judgment, language, and eventually the ability to carry out even the simplest of tasks.

"You just feel that you are half a person," Henderson says in his narrative, which was dictated on a tape recorder in the early stages of the disease. "And you so often feel that you are stupid for not remembering things or for not knowing things... Just the knowledge that I've goofed again or I said something wrong or I feel like I did something wrong or that I didn't know what I was saying or I forgot--all of these things are just so doggone common..."

Such personal accounts inevitably make one ask, why? What causes this disease? Can't anything be done to stop it? To prevent it? Scientists ask essentially the same questions, and this booklet describes their search for answers. It provides a brief overview of dozens of paths that are bringing us closer to ways of managing, and eventually defeating, Alzheimer's disease.

## Basics

A report like this one would not have been possible 20 years ago, when very little was known about Alzheimer's disease. But it is by no means a new disease. Ancient Greek and Roman writers described symptoms similar to those of Alzheimer's disease. In the 16th century, Shakespeare wrote about very old age as a time of "second childishness and mere oblivion," suggesting that the

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symptoms of Alzheimer's disease, or something quite similar, were known and recognized then.

These characteristic symptoms acquired a name in the early part of the 20th century when Alois Alzheimer, a German physician, described the signs of the disease in the brain. Alzheimer had a patient in her fifties who suffered from what seemed to be a mental illness. But when she died in 1906, an autopsy revealed dense deposits, now called neuritic plaques, outside and around the nerve cells in her brain. Inside the cells were twisted strands of fiber, or neurofibrillary tangles. Today, a definite diagnosis of Alzheimer's disease is still only possible when an autopsy reveals these hallmarks of the disease.

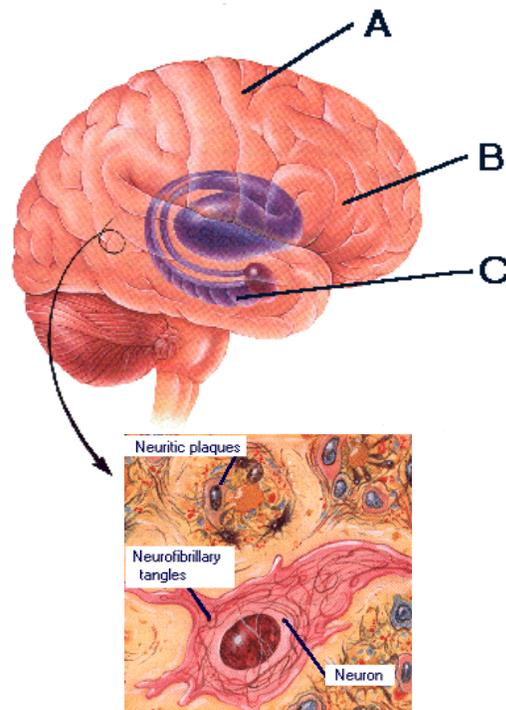
Plaques and tangles remained mysterious substances until the 1980's, when neuroscientists--the scientists who study the brain--discovered the proteins that make up these telltale anomalies. As research progresses, it is turning up clues to how plaques and tangles develop and how they relate to other changes in the brain.

In the meantime, much more about the disease has come to light. We now know that Alzheimer's begins in the entorhinal cortex and proceeds to the hippocampus, a waystation important in memory formation. It then gradually spreads to other regions, particularly the cerebral cortex. This is the outer area of the brain, which is involved in functions such as language and reason. In the regions attacked by Alzheimer's, the nerve cells or neurons degenerate, losing their connections or synapses with other neurons. Some neurons die.

### The Brain and Alzheimer's Disease

Alzheimer's disease attacks nerve cells in several regions of the brain.

- A. Cerebral Cortex:  
Involved in conscious thought and language.
- B. Basal forebrain:  
Has large numbers of neurons containing acetylcholine, a chemical important in memory and learning
- C. Hippocampus:  
Essential to memory storage.



**The Brain and Alzheimer's Disease--Shows the cerebral cortex, involved in conscious thought and language; the basal forebrain, which has large numbers of neurons containing acetylcholine, a chemical important in memory and learning; the hippocampus, which is essential to memory storage; neuritic plaques; and neurofibrillary tangles. Alzheimer's disease attacks nerve cells (neurons) in several regions of the brain. The earliest signs of Alzheimer's are found in the nearby entorhinal cortex (not shown). Hallmarks of Alzheimer's disease include neuritic plaques (outside neurons), and neurofibrillary tangles (inside neurons).**

## The course of the disease.

As the hippocampal neurons degenerate, short-term memory falters. Often the ability to perform routine tasks begins to deteriorate as well. Henderson describes the difficulty and frustration he feels when he tries to open a can of food for the family's dog. "...the best I could do was to try to dig a hole, make a little perforation and see if I could extend the side of it--and it was something like a panic...I'm too clumsy because of the Alzheimer's.... Right now, the doggie seems to be in fairly good shape. I'm not too sure I am."

As Alzheimer's disease spreads through the cerebral cortex, it begins to take away language. "Lately, I've had trouble with words (practically have to play charades)" says Letty Tennis, a North Carolina woman with Alzheimer's disease who also kept a journal.

Tennis talks about how her judgment is changing and refers to the emotional outbursts that are common in this disease. "We had a great time shopping, but...I bought everything in sight....My poor dear husband didn't stop me very much unless it was too outrageous and then I'd get very angry. I bought a pair of boots--galoshes really...and I told George it's something I've always wanted so we bought them and when we got home I had no memory of buying them--they were awful and cost \$40...I used to be the sensible one in the family."

Disturbing behaviors, such as wandering and agitation, beset many people as the disease progresses. In its final stages Alzheimer's disease wipes out the ability to recognize even close family members or to communicate in any way. All sense of self seems to vanish, and the individual becomes completely dependent on others for care.

Patients often live for years with this condition, dying eventually from pneumonia or other diseases. The duration of Alzheimer's disease from time of diagnosis to death can be 20 years or more. The average length is thought to be in the range of 4 to 8 years.

### Definitions

**Dementia:** A group of symptoms characterized by a decline in intellectual functioning severe enough to interfere with a person's normal daily activities and social relationships. Alzheimer's Disease: The most common cause of dementia among older people. It is marked by progressive, irreversible declines in memory, performance of routine tasks, time and space orientation, language and communication skills, abstract thinking, and the ability to learn and carry out mathematical calculations. Other symptoms of Alzheimer's disease include personality changes and impairment of judgment.

**Age-Associated Memory Impairment:** A decline in short-term memory that sometimes accompanies aging; also called benign senescent forgetfulness. It does not progress to other cognitive impairments as Alzheimer's disease does.

**Senile Dementia:** An outdated term once used to refer to any form of dementia that occurred in older people.

## Progress

This bleak picture is countered by the continued, rapid pace of research. Many neuroscientists think that a means to prevent or treat Alzheimer's disease will be found in the foreseeable future.

Studies of Alzheimer's disease can be divided into three broad, interacting categories. The first is research on causes, the second is diagnosis, and the third is treatment, which includes caregiving. The following chapters give a brief overview of what is known about each topic. They highlight some key findings to date, the clues researchers are now pursuing, and the paths that are expected to lead to answers about Alzheimer's disease.

### Further Reading

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Tennis L. "Alzheimer's Diary: I Have What!" *The Caregiver: Newsletter of the Duke Family Support Program* 12(1):6-13, 1992.

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## The Public Health Impact of Alzheimer's Disease

**How Many People...** It is estimated that about 4,000,000 people in the United States have Alzheimer's disease. This is a very rough estimate. Alzheimer's disease is not reported on death certificates, so estimates of prevalence (how many people have a disease at any one time) are based on surveys in different communities, and their findings vary. Most surveys have found the percentage of people age 85 and older who have any kind of dementia, including Alzheimer's, to be in the range of 25 to 35 percent. One study in Boston, however, found that the percentage of people with Alzheimer's disease alone was 47.2 percent in people age 85 and over.

One problem in getting accurate figures lies in the lack of a single definition of either dementia or Alzheimer's disease. Different surveys use different criteria for determining whether a person falls into one category or another. This is one reason their findings can be different. Another problem is that in all populations studied, a large proportion of people are unable or unwilling to participate in surveys of dementia.

Although there is still no agreement on the exact percentage of people with Alzheimer's disease or other dementia, all studies do project one picture clearly--the exponential rise of this disease with age. After age 65, the percentage of affected people approximately doubles with every decade of life, regardless of how a survey defines dementia or Alzheimer's disease.

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It is also clear that as America's older population grows, the number of people with Alzheimer's will rise. If current population trends continue and no cure is found, the actual number of people with the disease could double every 20 years.

...**And How Much It Costs.** Alzheimer's disease has been estimated to cost the nation \$80 to \$90 billion a year. This figure includes both direct financial outlays, such as for nursing care, as well as indirect costs, such as lost productivity on the part of patients and the family members who care for them.

Caring for a patient with Alzheimer's disease costs more than \$47,000 a year whether the person lives at home or in a nursing home, according to a recent study in northern California. This study found that the families of Alzheimer's disease patients living at home spent about \$12,000 annually, per family, for formal services, such as physician care and home health aides. But when the researchers added the estimated cost of unpaid, informal care provided by family members, the total annual cost was \$47,049--comparable to the cost of nursing home care.

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Rice D, Fox PJ, Max W, et al. The Economic Burden of Alzheimer's Disease Care, *Health Affairs*, 12(2):164-176, 1993.

## **The Search for Causes**

The brain has hundreds of billions of neurons, any one of which can have thousands, even hundreds of thousands, of connections with other neurons. Within and among their extensive branches travel dozens of chemical messengers--neurotransmitters, hormones, growth factors, and more--linking each neuron with others in a vast communications network.

Somewhere in this complex signaling system lies the cause of Alzheimer's disease. In the past two decades, neuroscientists have combed through it in search of defects that might explain what goes wrong in this disease. One of their earliest findings came from studies of neurotransmitters, the chemicals that relay messages between neurons.

### **Neurotransmitters**

Neurotransmitters reside in tiny sacs at the ends of axons, the long tube-like extensions of neurons. Released when electrical impulses pass along the axon, the chemicals cross a minute space called the synapse and bind to a molecule (a receptor) sitting in the membrane of the next neuron. The neurotransmitters then either break down or pass back into the first neuron, while other substances inside the second neuron take up and relay the message.

## Unraveling the Mystery

In the mid 1970's, scientists discovered that levels of a neurotransmitter called acetylcholine fell sharply in people with Alzheimer's disease. The discovery was intriguing for several reasons. Acetylcholine is a critical neurotransmitter in the process of forming memories. Moreover, it is the neurotransmitter used commonly by neurons in the hippocampus and cerebral cortex--regions devastated by Alzheimer's disease.

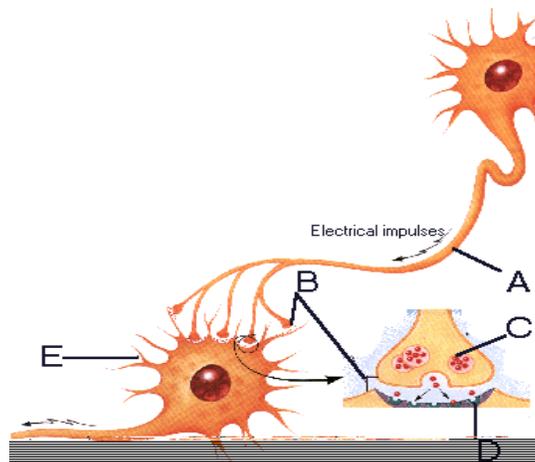
Since that early discovery, which was one of the first to link Alzheimer's disease with biochemical changes in the brain, acetylcholine has been the focus of hundreds of studies. Scientists have found that its levels fall somewhat in normal aging but drop by about 90 percent in people with Alzheimer's disease. They have turned up evidence linking this decline to memory impairment. And they have looked for ways to boost its levels as a possible treatment for Alzheimer's disease.

Other neurotransmitters have also been implicated in Alzheimer's disease. For example, serotonin, somatostatin, and noradrenaline levels are lower than normal in some Alzheimer's patients, and deficits in these substances may contribute to sensory disturbances, aggressive behavior, and neuron death. Most neurotransmitter research, however, continues to focus on acetylcholine because of its steep decline in Alzheimer's disease and its close ties to memory formation and reasoning.

### How Neurons Communicate

Neurotransmitters are released from the axon, cross the synapse, and bind to receptors on the surface of another neuron.

- A. Axon
- B. Synapse
- C. Vesicles containing neurotransmitter molecules
- D. Receptors
- E. Dendrites



**How Neurons Communicate--Shows cell bodies, axons, and dendrites of two neurons, the synapse between them, receptors, and vesicles containing neurotransmitter molecules; how neurotransmitters are released from the axon, cross the synapse, and bind to receptors on the surface of another neuron; and how electrical impulses pass along the axon.**

### On the Other Side of the Synapse

Once the message carried by a neurotransmitter has crossed the synapse it passes into another territory, where neuroscientists are beginning to find more clues to Alzheimer's disease. The gateways to this new territory are the receptors, coil-shaped proteins embedded in neuron membranes. They interest Alzheimer's researchers for two reasons.

First, these molecules have chemical bonds with molecules of fat, called phospholipids, that lie next to them in the membrane. Several studies have detected phospholipid abnormalities in neurons

## Alzheimer's Disease

affected by Alzheimer's disease. These abnormalities might change the behavior of neighboring receptors and garble the message as it passes from neuron to neuron.

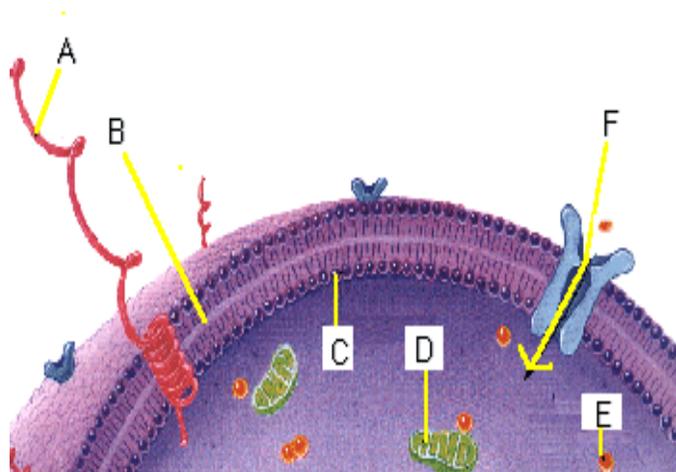
Second, researchers have uncovered several types of receptors for acetylcholine and are now exploring their different effects on message transmission. It may be that the shapes and actions of the receptors themselves, independent of their neighboring phospholipids, play a role in Alzheimer's.

But the receptor is just the starting point of the cell's communications system. When a neurotransmitter binds to a receptor, it triggers a cascade of biochemical interactions that relay the message to the neuron's nucleus, where it activates certain genes, or to the end of the axon, where it passes to other cells.

This messaging system involves a number of proteins, and abnormalities in these proteins or dysfunction at the relay points could block or garble the message. So could other events and processes in the cell, such as problems with the system that turns food into energy (metabolism) or the mechanisms that keep calcium levels in balance.

Drug therapies aimed at these various postsynaptic events are now being explored, although most are still in the very earliest phases of testing. Two of them, vitamin E and deprenyl, are currently in clinical trials (studies of people).

- A. Spiral shaped receptor
- B. Neuron membrane
- C. Phospholipid bilayer
- D. Mitochondria
- E. Cytoplasm
- F. Channel



**Across the Synapse--Problems in the membrane, or inner structures of the neuron receiving the message, may be involved in Alzheimer's disease. Shows a spiral shaped receptor, the neuron membrane, the phospholipid bilayer, mitochondria, cytoplasm, and membrane channels.**

## The Proteins

### Beta amyloid

When Alois Alzheimer observed the plaques now known as a hallmark of this disease, he could say little about them. No one knows still what role they play in the disease process, but scientists have learned that plaques are composed of a protein fragment called beta amyloid mixed with other proteins. Beta amyloid is a string of 40 or so amino acids snipped from a larger protein called amyloid precursor protein or APP.

Scientists also know something about how beta amyloid is formed. Its parent protein, APP, protrudes through the neuron membrane, part inside and part outside the cell. There only for a moment, it is continually replaced by new APP molecules manufactured in the cell. While it is embedded in the membrane, enzymes called proteases snip or cleave it in two, creating the beta amyloid fragment.

What happens to the beta amyloid segment once it separates from APP is less clear. A number of studies have centered on how beta amyloid is processed, searching for abnormalities that could explain what goes wrong. Others are seeking clues in the environment surrounding the protein. For instance, certain other substances in the neighborhood of beta amyloid protein may normally bind to it and thus keep it in solution. But in Alzheimer's disease, according to one theory, something causes the beta amyloid to drop out of solution and form the insoluble plaques.

Other areas of research center on how beta amyloid affects neurons--if at all. In one laboratory study, hippocampal neurons died when beta amyloid was added to the cell culture, suggesting that the protein is toxic to neurons. Another recent study suggests that beta amyloid breaks into fragments, releasing free radicals that attack neurons.

The precise mechanism by which beta amyloid might cause neuron death is still a mystery, but one recent finding suggests that beta amyloid forms tiny channels in neuron membranes. These channels may allow uncontrolled amounts of calcium into the neuron, an event that can be lethal in any cell.

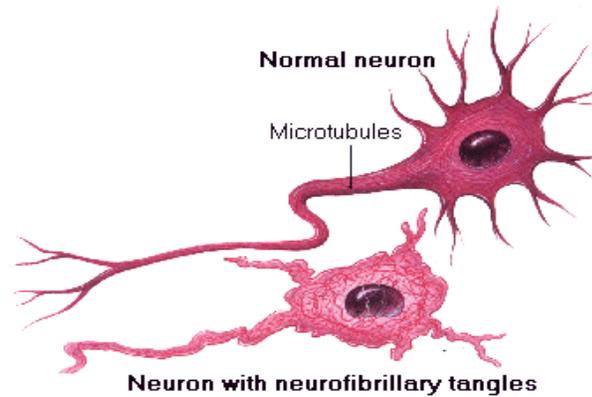
Other recent studies suggest that beta amyloid disrupts potassium channels, which could also affect calcium levels. Still another study links beta amyloid to reduced choline concentrations in neurons; since neurons need choline to synthesize acetylcholine, this finding suggests a link between beta amyloid and the death of cholinergic neurons.

### Tau

Another set of clues centers on a protein called tau, the major component of neurofibrillary tangles.

Neurofibrillary tangles resisted analysis until the late 1980's, when researchers discovered they were associated with neurons' internal structures, called microtubules. In healthy neurons, microtubules are formed like train rails, long parallel tracks with crosspieces, that carry nutrients from the body of the cells down to the ends of axons. In cells affected by Alzheimer's, this structure has collapsed. Tau normally forms the crosspieces between microtubules, but in Alzheimer's it twists into paired helical filaments, like two threads wound around each other. These are the basic constituents of neurofibrillary tangles.

## Alzheimer's Disease



**Compares a normal neuron and its microtubules with a neuron with neurofibrillary tangles.**

Having identified beta amyloid and tau, researchers would now like to find out what they do in the brain and in Alzheimer's disease. Some ideas about their functions may come from studies of certain genes.

## The Genes

Located along the DNA in the nucleus of each cell, genes direct the manufacture of every enzyme, hormone, growth factor, and other protein in the body. Genes are made up of four chemicals, or bases, arranged in various patterns. Each gene has a different sequence of bases, and each one directs the manufacture of a different protein. Even slight alterations in the DNA code of a gene can produce a faulty protein. And a faulty protein can lead to cell malfunction and eventually disease.

Genetic research has turned up evidence of a link between Alzheimer's disease and genes on three chromosomes--14, 19, and 21. The apoE4 gene on chromosome 19 has been linked to late-onset Alzheimer's disease, which is the most common form of the disease.

### **ApoE4 and Alzheimer's disease.**

The apoE4 gene came to light through long, patient detective work topped off by the serendipity that sometimes occurs in science. Alzheimer's researchers knew there were families in which many members developed the disease late in life. And therefore they knew there had to be a gene that the affected family members had in common. Searching for this gene, they combed through the DNA from these families and by 1992 had narrowed the search down to a region on chromosome 19.

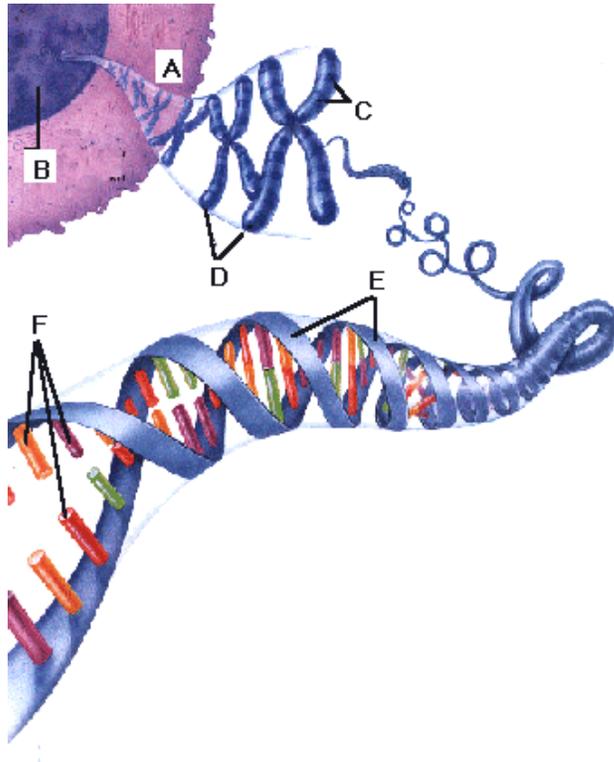
In the same laboratory, another group of researchers were looking for proteins that bind to beta amyloid. They were disappointed at first. One version of a protein called apolipoproteinE (apoE) did bind quickly and tightly to beta amyloid, but apolipoproteinE was well known as a carrier of cholesterol in blood. No one suspected that it could have anything to do with Alzheimer's disease.

## Unraveling the Mystery

But by coincidence, or so it seemed, the gene apoE, which produces the protein, was also on chromosome 19. Moreover, it was on the same region of chromosome 19 as the Alzheimer's gene for which they had been searching.

The two groups of scientists decided to see if the apoE gene and the still missing Alzheimer's gene could be one and the same, and what they found made headlines: The apoE gene was identical to the gene they had been seeking. ApoE, it turned out, is much more common among Alzheimer's patients than among the general population.

- A. Cell
- B. Nucleus
- C. Genes
- D. Chromosomes
- E. Double DNA strands
- F. Bases



Every cell in the body contains a nucleus which has 23 pairs of chromosomes.

Genes are made up of bases arranged in certain sequences.

**Chromosomes and Genes--Shows a nerve cell, chromosomes, genes, double DNA strands, bases, and a nucleus. Chromosomes contain DNA, or deoxyribonucleic acid, a large double-stranded molecule that includes genes. Every cell in the body contains a nucleus which has 23 pairs of chromosomes. Genes are made up of bases arranged in certain sequences.**

## Alzheimer's Disease

More precisely, one version of apoE is more common among Alzheimer's patients. Like some other genes, the one that produces apoE comes in several forms or alleles. The apoE gene has three different forms--apoE2, apoE3, and apoE4. ApoE3 is the most common in the general population. But apoE4 occurs in approximately 40 percent of all late-onset Alzheimer's patients. Moreover, it is not limited to people whose families have a history of Alzheimer's. Patients with no known family history of the disease, cases of so-called sporadic Alzheimer's disease, are also more likely to have an apoE4 gene.

Since that finding, dozens of studies around the world have confirmed that the apoE4 allele increases the risk of developing Alzheimer's disease. People who inherit two apoE4 genes (one from the mother and one from the father) are at least eight times more likely to develop Alzheimer's disease than those who have two of the more common E3 version. The least common allele, E2, seems to lower the risk even more. People with one E2 and one E3 gene have only one-fourth the risk of developing Alzheimer's as people with two E3 genes.

What does the apoE4 gene do? On one level, all genes function by transcribing their codes into proteins, so when we ask what a gene does, we are really asking what its protein product does. Many laboratories are now exploring what the apoE4 product does, and they have several clues.

Some of these clues point to beta amyloid. While the apoE4 protein binds rapidly and tightly to beta amyloid, the apoE3 protein does not. Normally beta amyloid is soluble, but when the apoE4 protein latches on to it, the amyloid becomes insoluble. This may mean that it is more likely to be deposited in plaques. Studies of brain tissue suggest that apoE4 increases deposits of beta amyloid and that it directly regulates the APP protein from which beta amyloid is formed.

Other clues, however, point to tau as the pivotal protein. As the crosspiece in the microtubule, tau's function seems to be to stabilize the microtubule structure. One hypothesis suggests that the apoE4 protein allows this structure to come undone in some way, leading to the neurofibrillary tangles.

While still controversial and far from proven, the hypotheses surrounding apoE4 are driving new research. One next step is to see how tau and beta amyloid react with apolipoprotein in its several forms in living cells. Other experiments will attempt to determine the actions and role of the protein. Once these are clear, it should be easier to see how they might be affected by drugs. For instance, if apoE2 does turn out to be beneficial, then substances that mimic its effects might be designed to help prevent or slow the progress of Alzheimer's disease.

The theories surrounding apoE4 are not confined to the proteins. One finding that intrigues neuroscientists is that Alzheimer's patients with the apoE4 gene have neurons with shorter dendrites--the branchlike extensions that receive messages from other neurons. Researchers speculate that the dendrites have been pruned back by some unknown agent, limiting the neuron's ability to communicate with other neurons. Although this pruning can also occur in people without the apoE4 allele, it happens 20 or 30 years earlier in people with apoE4.

Will the genetic information available now ever be used in screening for Alzheimer's disease? Probably not. One of the puzzles surrounding apoE4 is why some people with the gene do not develop Alzheimer's disease and why, conversely, many people develop the disease even though they do not have the gene. ApoE4, in other words, is not a consistent marker for Alzheimer's.

## Unraveling the Mystery

This is one reason that few people advocate widespread screening for apoE4. Screening would miss a large percentage of those who will develop Alzheimer's and falsely identify others as future Alzheimer's patients. Some scientists suggest, however, that testing for the gene may someday help in the diagnosis of Alzheimer's.

### **Genes in early-onset Alzheimer's disease.**

Two families in Belgium can count back six or seven generations in which some members developed Alzheimer's disease in their 30's and 40's. A Japanese family has 5 members who developed the disease in middle age; a Hispanic family has 12 members; a French-Canadian family, 23; a British family, 8. In families descended from Volga Germans--a group of German families that settled in the Volga River valley in Russia in the 1800s--dozens of descendants have developed Alzheimer's disease in middle age.

Alzheimer's strikes early and fairly often in these and other families around the world--often enough to be singled out as a separate form of the disease and given a label: early-onset familial Alzheimer's disease or FAD. Combing through the DNA of these early-onset families, researchers have found a mutation in one gene on chromosome 21 that is common to a few of the families. And they have linked a much larger proportion of early-onset families to a recently-identified gene on chromosome 14. The gene on chromosome 21 occurs less often in people with FAD than the chromosome 14 gene, which codes for a membrane protein whose function is not yet known.

The chromosome 21 gene carries the code for a mutated form of the amyloid precursor protein, APP, the parent protein for beta amyloid. The discovery of this gene supports the theory that beta amyloid plays a role in Alzheimer's disease, although the mutation occurs in only about 5 percent of early-onset families.

The chromosome 21 gene intrigues Alzheimer's researchers also because it is the gene involved in Down syndrome. People with Down syndrome have an extra version of chromosome 21 and, as they grow older, usually develop plaques and tangles like those found in Alzheimer's disease.

Few researchers think that the search for Alzheimer's genes is over. The Volga Germans, for one thing, have neither the chromosome 14 nor the chromosome 21 abnormality. Most investigators are convinced that there are several genes involved in Alzheimer's disease and, moreover, that other conditions must also be present for the disease to develop. One of these conditions may be a problem with the way in which neurons turn sugar, or glucose, into energy, a process known as glucose metabolism.

### **Metabolism**

Every few months, Alzheimer's patients travel to the National Institutes of Health outside of Washington, D.C., and to other centers around the country to take part in research studies. One of the tests they take measures brain activity using special techniques, such as PET (short for positron emission tomography).

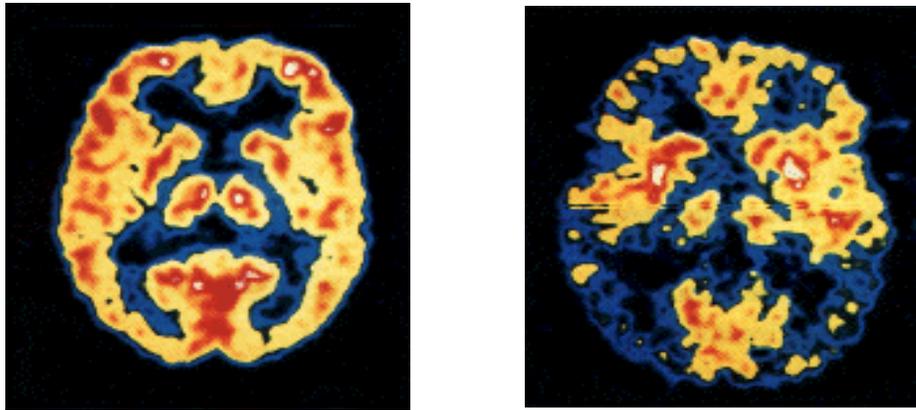
PET works on a simple principle. Brain activity, whether one is looking at a picture, working out

## Alzheimer's Disease

a problem in calculus, or simply observing the surroundings, requires energy. Neurons produce energy through metabolism, a chain of biochemical reactions that uses large amounts of glucose and oxygen. PET can track the flow of glucose and oxygen molecules in the bloodstream to the parts of the brain producing energy, thus revealing which areas are active.

A patient having a PET scan rests on a long low platform as the scanner tracks the flow of glucose or oxygen. The data the scanner collects are fed into a computer program which translates it into multicolor images: red and orange for areas of high activity, yellow for medium, blue and black for little or none.

By deciphering these patterns, Alzheimer's researchers can chart the progress of the disease. Glucose metabolism declines dramatically as neurons degenerate and die. Scientists are also using PET to learn how changes in brain activity match up with changes in skills, such as the ability to do arithmetic or to remember names of objects.



**Brain Metabolism in Alzheimer's Disease. PET scans show differences in brain activity between a normal brain (left) and a brain affected by Alzheimer's disease (right). Blue and black denote inactive areas.**

No one knows whether the decline in glucose metabolism causes neurons to degenerate or whether neuron degeneration causes metabolism to decline. In the effort to find out, scientists have examined glucose molecules at every step of the way from bloodstream to neuron.

The route is complex. It begins as glucose-laden blood flows through the capillaries, the tiny blood vessels that carry the blood past neurons. Specialized molecules capture glucose molecules from blood and shuttle them into the neurons.

These transporter molecules come in several forms. One recent study found that levels of two of them, GLUT1 and GLUT3, were low in the cerebral cortex of people with Alzheimer's disease. These reductions could be one reason glucose metabolism drops in Alzheimer's.

Another key element in this scenario could be the condition of the capillaries. The transport system could break down because of thickening of the capillary walls, deposits of minerals, cholesterol, and amyloid, or some injury to these microvessels.

## Unraveling the Mystery

Once inside the cell, glucose molecules are delivered to inner structures, called mitochondria, where they are turned into energy through metabolism. This process involves various enzymes and other proteins, as well as glucose and oxygen. An alteration in any of the ingredients could have a profound effect on the end result, so investigating these enzymes is another important area in Alzheimer's research. Studies have found, for instance, that the enzyme cytochrome oxidase, important in glucose metabolism, is produced at lower levels in cells affected by Alzheimer's. Since its decline matches the declines in glucose metabolism, it may play a role in the disease.

While the glitch in glucose metabolism has yet to be pinpointed, its results are known to be devastating. Neurons depend wholly on glucose for their sustenance and when glucose metabolism falters, they suffer in various ways. For example, they cannot manufacture as much acetylcholine as normal cells, which may be one reason this neurotransmitter declines in Alzheimer's.

In addition, neurons having a problem with metabolism react abnormally to another neurotransmitter, called glutamate. When these neurons are stimulated by glutamate--even normal amounts of glutamate--their regular mechanisms go awry and they are flooded by calcium, with deadly consequences.

## The Calcium Hypothesis

Calcium is an important substance in certain cells of the body, the so-called excitable cells in muscles and the nervous system. Muscle cells need calcium to contract, neurons to transmit signals. Normally, the amount of calcium in a cell at any one time is carefully regulated; calcium channels allow in certain amounts of calcium at certain times, other proteins store the calcium within the cell or remove it. Too much calcium can kill a cell, and some neuroscientists suspect that in the end, a rise in calcium levels may be precisely what is killing neurons in Alzheimer's disease. According to one hypothesis, an abnormally high concentration of calcium inside a neuron is the final step in cell death. Several different series or cascades of biochemical events could lead up to this last, fatal step.

What events might these be? One possibility is that an increase in calcium channels could allow an excess of calcium into the cell. Another possibility is that a defect develops in the structures that store calcium inside the cell or those that pump it out of the cell.

Still another hypothesis suggests that calcium levels rise because of an "energy crisis" in the neuron. In this scenario, chronically high levels of the neurotransmitter glutamate disrupt energy metabolism, leading to an influx of calcium. Glutamate is an excitatory neurotransmitter; it triggers action in a neuron, stimulating the flow of calcium into the cell. If it is produced in higher-than-normal levels, it can overexcite a neuron, driving in too much calcium. Moreover, glutamate can be dangerous to a neuron even at normal levels if glucose levels are low. Thus a problem with glucose metabolism could allow glutamate to overexcite the cell, allowing an influx of calcium.

Another hypothesis, involving the hormones called glucocorticoids, ties in with this theory. Glucocorticoids normally enhance the manufacture of glucose and reduce inflammation in the body. They came to the attention of Alzheimer's researchers when studies in older animals showed that long exposure to glucocorticoids contributed to neuron death and dysfunction in the hippocampus.

## Alzheimer's Disease

Now several laboratories are exploring mechanisms by which glucocorticoids might lead to neuron death through their effect on glucose metabolism.

### **Environmental Suspects**

No one doubts that genetic and other biological factors are important in Alzheimer's disease, but environmental factors could also contribute to its development. The most studied of these are aluminum, zinc, foodborne poisons, and viruses.

#### **Aluminum.**

One of the most publicized and controversial hypotheses in this area concerns aluminum, which became a suspect in Alzheimer's disease when researchers found traces of this metal in the brains of Alzheimer's patients. Many studies since then have either not been able to confirm this finding or have had questionable results.

Aluminum does turn up in higher amounts than normal in some autopsy studies of Alzheimer's patients, but not in all. Further doubt about the importance of aluminum stems from the possibility that the aluminum found in some studies did not all come from the brain tissues being studied. Instead, some could have come from the special substances used in the laboratory to study brain tissue.

Aluminum is a common element in the Earth's crust and is found in small amounts in numerous household products and in many foods. As a result, there have been fears that aluminum in the diet or absorbed in other ways could be a factor in Alzheimer's. One study found that people who used antiperspirants and antacids containing aluminum had a higher risk of developing Alzheimer's. Others have also reported an association between aluminum exposure and Alzheimer's disease.

On the other hand, various studies have found that groups of people exposed to high levels of aluminum do not have an increased risk. Moreover, aluminum in cooking utensils does not get into food and the aluminum that does occur naturally in some foods, such as potatoes, is not absorbed well by the body. On the whole, scientists can say only that it is still uncertain whether exposure to aluminum plays a role in Alzheimer's disease.

#### **Zinc**

Zinc has been implicated in Alzheimer's disease in two ways. Some reports suggest that too little zinc is a problem, others that too much zinc is at fault. Too little zinc was suggested by autopsies that found low levels of zinc in the brains of Alzheimer's disease patients, especially in the hippocampus.

On the other hand, a recent study suggests that too much zinc might be the problem. In this laboratory experiment, zinc caused soluble beta amyloid from cerebrospinal fluid to form clumps similar to the plaques of Alzheimer's disease. Current experiments with zinc are pursuing this lead in laboratory tests that more closely mimic conditions in the brain.

### **Foodborne poisons.**

Toxins in foods have come under suspicion in a few cases of dementia. Two amino acids found in seeds of certain legumes in Africa, India, and Guam may cause neurological damage. Both enhance the action of the neurotransmitter glutamate, also implicated in Alzheimer's disease.

In Canada, an outbreak of a neurological disorder similar to Alzheimer's occurred among people who had eaten mussels contaminated with domoic acid. This chemical, like the legume amino acids, is a glutamate stimulator. While these toxins may not be a common cause of dementia, they could eventually shed some light on the mechanisms that lead to neuron degeneration.

### **The search for a virus.**

In some neurological diseases a virus is the culprit, lurking in the body for decades before a combination of circumstances stirs it to action. So for years researchers have sought a virus or other infectious agent in Alzheimer's disease.

This line of research has yielded little in the way of hard evidence so far, although one study in the late 1980's did provide some data that have kept the possibility alive. A larger investigation is now under way.

## **Alzheimer's Risk Factors and the Search for Causes**

One tool in the search for causes of disease is the study of risk factors. Similarities among people with a certain disease may be risk factors, and they can provide clues to what is going wrong. For example, when a sizable group of Alzheimer's patients all come from the same family, epidemiologists suspect that a gene is at fault.

Epidemiologic studies also search for environmental causes of disease. For example, one current study is comparing a group of Alzheimer's patients in Nigeria to a group of African-Americans with Alzheimer's disease. If the prevalence is higher in one group than another, the scientists will then look for some factor in the environment that could explain the difference.

So far, only two risk factors have been linked to Alzheimer's disease. Others are under investigation.

### **Known risk factors**

**Age:** The risk of Alzheimer's rises exponentially with age, doubling in each decade after age 65.

**Family history/genetic disposition:** People with relatives who developed Alzheimer's disease are more likely to develop the disease themselves. So far, scientists have discovered three genes

## Alzheimer's Disease

that help explain why family history is a risk factor.

### **Possible risk factors**

**Head injury:** Some studies have found that Alzheimer's disease occurs more often among people who suffered traumatic head injuries earlier in life. A major survey of World War II veterans is now looking for more evidence to corroborate this finding.

**Gender:** Women may have a higher risk of the disease, although their higher rates may only reflect the effects of age--women have longer life spans on the average than men.

**Educational level:** Research suggests that the more years of formal education a person has, the less likely he or she is to develop Alzheimer's later in life. Thus lower educational levels may increase the risk.

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## **A Disease With Many Causes?**

The trails of clues that Alzheimer's leaves in its wake have so far not converged. When they do, some scientists think that this detective story will turn out to have a number of culprits. One theory suggests that several factors act in sequence or in combination to cause Alzheimer's disease, even though no single factor is sufficient by itself. To explain this idea, scientists use the metaphor of a light that requires several switches. There might, for example, be just two switches, such as a gene mutation and another event to trigger the gene. Or there might be several. According to this idea, called the AND gate theory, these events do not have to occur at the same time, but their effects would have to linger and eventually coincide to bring about Alzheimer's disease.

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## **Research on Diagnosis**

Ken Judy remembers vividly the first signs that something was wrong. "Bernice began to forget appointments or what she had planned for the day," he says. "She would lose her train of thought in the middle of a sentence. She began to withdraw from society. She didn't want to volunteer at the hospital or go to her church group."

Bernice Judy had a range of medical tests that suggested she had Alzheimer's disease or a related disorder. The diagnosis, in her case, turned out to be Pick's disease, another brain disease that is similar in many ways to Alzheimer's.

Ten years earlier Bernice Judy's illness would probably have been swept into a broad and ill-defined category labeled senile dementia. But with the recognition of Alzheimer's as a distinct and common disease, progress in diagnosing it has been rapid. Alzheimer's researchers are still some way from their ultimate aim--a reliable, valid, inexpensive, and early diagnostic marker--but they now have the tools to diagnose the disease with 85 to 90 percent accuracy.

Despite the lack of a treatment for Alzheimer's, early diagnosis has advantages. Twenty percent of suspected Alzheimer's cases turn out to be something else, and it is often something that can be treated or even reversed. Tumors, strokes, severe depression, thyroid problems, medication side effects (or "drug intoxication"), nutritional disorders, and certain infectious diseases can all have effects that mimic those of Alzheimer's. Early diagnosis increases the chances of treating these conditions successfully.

Even when the underlying cause of dementia turns out to be Alzheimer's, there are advantages to finding out sooner rather than later. One benefit is medical. The only drug now on the market to treat the cognitive decline in Alzheimer's disease, THA, is more likely to be effective in the early stages of the disease. The same may be true of other drugs now being developed.

## Unraveling the Mystery

Other advantages to an early diagnosis are practical ones. The sooner the patient and family know, the more time there is to make future living arrangements, handle financial and legal matters, and establish a support network.

Research on diagnosis falls into two categories. One major group of studies is looking for early biological markers--changes in blood chemistry or brain structures, for example. Another group is searching for telltale changes in mental abilities and personality--the so-called cognitive markers.

### **Cognitive Markers**

When Bernice Judy went to a doctor about her memory problems, one of the tests consisted of 10 simple questions, such as: What day is this? Where are we? Who is the President of the United States? This brief mental status questionnaire is one way to look for cognitive markers of Alzheimer's, but it is far from definitive.

More reliable cognitive markers are urgently needed. In the search for them, scientists are studying a phenomenon known as visual memory--the ability to remember and reproduce geometric patterns, for instance. People who develop Alzheimer's disease begin to lose immediate visual memory sooner than is expected in normal aging and long before other markers of dementia appear, according to some studies. Declines in verbal memory also may be an early marker.

Followup studies are now looking for such markers in larger groups of people. They are also using brain imaging techniques, such as PET scans and MRI, to see if early cognitive markers can be linked to early biological changes in the brain.

The familiar visual pattern of a clock forms the basis of one experimental method of diagnosing Alzheimer's. In this test, the patient draws the face of a clock, draws the hands to show certain times, and reads the time when someone else draws the hands. So far, findings suggest that the clock test may help differentiate Alzheimer's from the effects of normal aging and perhaps from other forms of dementia. Larger studies will follow up on this lead.

Other researchers are searching for changes in personality that may herald the onset of Alzheimer's. In normal aging, personality does not change with age. In Alzheimer's, however, there is a hint that two facets of personality may change early in the disease; these are "conscientiousness," which declines and "vulnerability to stress," which increases. These findings are far from conclusive, but they do offer a lead. Researchers are following up by tracking personality changes in a larger group.

### **Diagnosing Alzheimer's Disease: Current Tools**

A definite diagnosis of Alzheimer's disease is still only possible during autopsy when the hallmark plaques and tangles can be detected. But with the tools now available, physicians and patients can count on 85 to 90 percent accuracy, according to studies in which clinical diagnosis was later confirmed by autopsy. Clinicians diagnose "possible Alzheimer's disease" and "probable Alzheimer's disease" using criteria established in 1984 by the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Diseases Association (NINCDS/ADRDA Guidelines).

## Diagnostic Tools

**Patient history:** A detailed description of how and when symptoms developed; the patient's and family's medical history; and an assessment of the patient's emotional status and living environment.

**Physical examination and laboratory tests:** Standard medical tests to help identify other possible causes of dementia.

**Brain scans:** Usually a computed tomography (CT) scan or magnetic resonance imaging (MRI) to detect strokes or tumors that could be causing symptoms of dementia.

**Neuropsychological testing:** Usually several different tests in which patients answer questions or complete tasks that measure memory, language skills, ability to do arithmetic, and other abilities related to brain functioning.

## Biological Markers

The tantalizing possibility that somewhere outside the brain there is a biological marker for Alzheimer's disease--an abnormal protein, for instance, that shows up in blood as well as the brain--continues to attract investigators.

Over the past decade, small preliminary studies have raised hope--and headlines--for several different markers. So far none has stood up under closer scrutiny. Still under consideration is a marker that may show up during a simple eye test, according to one study. In this study, a drug commonly used in eye examinations to enlarge the pupils, called tropicamide, increased the pupil size of suspected Alzheimer's disease patients in the study more than in other older people. This study involved fewer than 20 patients. Again, the next step is larger studies.

## Imaging

Scans of the brain already help in diagnosing Alzheimer's disease by ruling out other forms of dementia, such as tumors and signs of stroke. But researchers also are using scans to search for markers of Alzheimer's disease itself.

Their tools include PET, which traces blood flow and metabolism in the brain and SPECT (single photon emission computed tomography) which also measures blood flow. Another imaging technique, magnetic resonance imaging (MRI), lets researchers view the brain's structure in cross section.

New techniques available to PET and SPECT researchers allow them to assess interactions among molecules in the brain, such as neurotransmitters and their receptors. Another new technique, magnetic resonance spectroscopy imaging or MRSI, lets neuroscientists observe certain substances throughout the brain, without using radioactive markers.

## Unraveling the Mystery

All of the imaging techniques--PET, SPECT, MRI, and MRSI--are still primarily research tools. However, they hold the promise of leading to an early and cost-effective method for diagnosing Alzheimer's disease.

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## Investigating Treatments

The rapid pace of research on Alzheimer's disease over the past 20 years has opened numerous pathways that could lead to effective treatments for the disease. Treatment research falls into two general categories. First, neuroscientists have turned up an array of substances in the brain that seem to be related to the disease and these are potential targets for biomedical treatments.

A second group of studies focuses on management of the disease. This area of research is looking for ways to treat the symptoms of Alzheimer's disease and slow its progress, either through drugs or behavioral approaches.

## Potential Biomedical Treatments

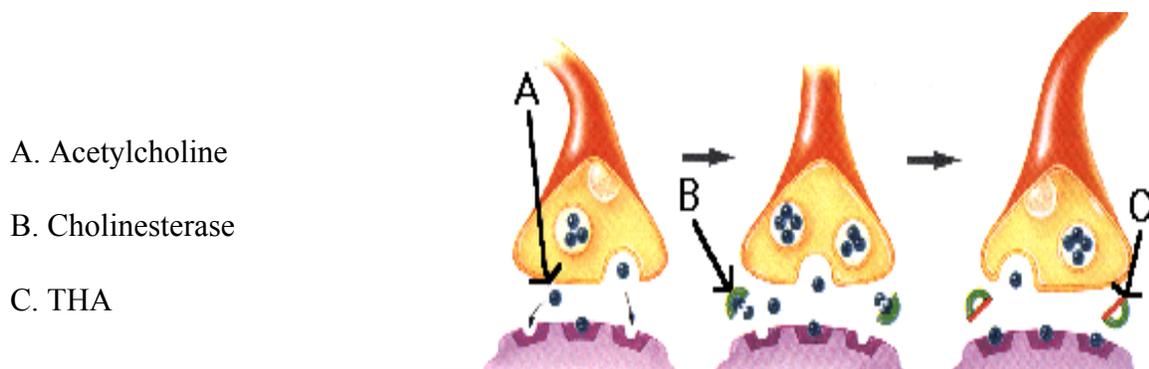
### Cholinergic replacement therapy.

The discovery that the neurotransmitter acetylcholine declines in Alzheimer's disease led naturally to the hypothesis that replacing acetylcholine could stop the disease. Since that finding, many scientists have looked for compounds that can either increase the levels of acetylcholine, replace it, or slow its breakdown. This search has taken them into a broader territory that includes the cells that use acetylcholine and the enzymes and other proteins that take part in its manufacture or activity--a grouping known as the cholinergic system.

One member of the cholinergic system is acetylcholinesterase (often referred to simply as cholinesterase), the enzyme that breaks down acetylcholine after it crosses the synapse. Many of the experimental Alzheimer's drugs developed to date are cholinesterase inhibitors; that is, they are designed to suppress cholinesterase so that acetylcholine will not be broken down as quickly.

One such cholinesterase inhibitor is THA or tetrahydroaminoacridine, the only drug approved so far by the Food and Drug Administration to slow the loss of cognitive ability in Alzheimer's disease. THA has helped some patients, but its impact on the disease in general has proved disappointing. However other cholinesterase inhibitors that may be more effective are under development.

The discovery of acetylcholine deficits in Alzheimer's disease also raised hope that choline and lecithin, if added to the diet, could help in treating Alzheimer's disease. The body uses these nutrients to synthesize acetylcholine. Trials with the two substances have been disappointing so far, with choline supplements having no effect on cognitive function and lecithin only a slight effect in a few patients. Researchers are still interested in other substances that may enhance the availability of acetylcholine.



**How THA Works--Cholinesterase inhibitors (red) like THA, block cholinesterase, giving the acetylcholine extra time to transmit messages. Normally acetylcholine carries a message across the synapse... and then is broken down by cholinesterase.**

### **Neurotrophic factors**

When a laboratory animal makes its way through a maze to get to a reward, it makes a number of wrong turns the first time. After that, its errors are fewer, and it makes more correct turns. Scientists have various ways to explain what is happening in the animal's brain in such experiments, but in simple terms, the animal is remembering.

Some older rats (about 2 years old) take longer to negotiate a maze or cannot seem to make memories of the correct turns at all. In a study in the mid-1980's, scientists took several rats with such memory impairment and gave them nerve growth factor or NGF. The rats' ability to negotiate the maze improved, coming close to the ability seen in older rats with no impairment. Because of this study and several similar ones, NGF intrigues neuroscientists as a possible treatment for Alzheimer's disease.

How NGF works is not completely clear, but it is known to be one of several growth factors in the brain or, in neurobiologists' terms, neurotrophic factors. Growth factors elsewhere in the body promote and support cell division. Neurons cannot divide, but they can regenerate after injury and neurotrophic factors promote this regeneration. They also promote the growth of axons and dendrites, the neuron branches that form connections with other neurons. Other neurotrophic factors that may be implicated in Alzheimer's include brain derived neurotrophic factor and neurotrophin-3.

Studies have turned up a number of clues that link NGF specifically to the cholinergic neurons (those that use acetylcholine as a neurotransmitter). In that early maze experiment, the rats whose memories had improved not only had higher NGF levels but also their cholinergic neurons had regenerated. In another study, NGF promoted the survival of cholinergic neurons after injury.

## **Symptoms of Alzheimer's Disease**

Alzheimer's is a progressive disease, the symptoms growing worse with time. Yet it is also a variable disease. Symptoms progress at different rates and in different patterns. Thus one patient may begin to have problems with muscular coordination earlier than another or retain some memories longer.

Researchers, who need to have some standard way to measure the progression of symptoms, have devised several different scales. One, the Clinical Dementia Rating (CDR), delineates five stages in the disease, while another, the Global Dementia Scale (GDS), has seven stages.

However most people who work with patients and families think of the disease in three phases: mild, moderate, and severe. These three stages can be viewed as follows, keeping in mind that the divisions are approximate, that they overlap, and that the appearance and progression of symptoms vary from one individual to the next.

## Alzheimer's Disease

### **Mild Symptoms**

- Confusion and memory loss
- Disorientation; getting lost in familiar surroundings
- Problems with routine tasks
- Changes in personality and judgment

### **Severe Symptoms**

- Loss of speech
- Loss of appetite; weight loss
- Loss of bladder and bowel control
- Total dependence on caregiver

### **Moderate Symptoms**

- Difficulty with activities of daily living, such as feeding and bathing
- Anxiety, suspiciousness, agitation
- Sleep disturbances
- Wandering, pacing
- Difficulty recognizing family and friends

### **Source:**

Gwyther LP. Care of Alzheimer's Patients: A Manual for Nursing Home Staff, Chicago: American Health Care Association and Alzheimer's Disease and Related Disorders Association, 1985.

### **Getting around the blood-brain barrier.**

The problem in testing NGF in humans is the difficulty getting it into the brain. While substances pass easily from the bloodstream to cells in other parts of the body, the brain has a complex set of defenses that protect it from possible poisons. Known as the blood-brain barrier, these defenses include physical barriers, such as tightly opposed cells in the walls of the blood vessels. Another defense is chemical--enzymes that act as gatekeepers, escorting only certain substances into the inner compartments.

One way to circumvent the blood-brain barrier is through direct injections into the brain, but there is little evidence that such injections are effective. So researchers have been looking at other ways to deliver drugs to the brain. Animal experiments with the NGF gene show that it can be incorporated into skin cells and then implanted in brains, where it has prevented the loss and degeneration of cholinergic neurons. Other researchers are looking at ways to package NGF and other neurotrophic factors with substances that can cross the blood-brain barrier, in effect smuggling these potential treatments into the brain.

Researchers are also investigating substances that interact with NGF. One of these is estrogen, the female reproductive hormone that falls sharply at menopause.

### **Estrogen replacement**

Estrogen made front page headlines in late 1993 when scientists reported a possible link between it and Alzheimer's disease. In a study of thousands of women in a southern California retirement community, those who had taken estrogen after menopause had lower rates of Alzheimer's disease than those who had not taken estrogen.

It was not the first time that neuroscientists had taken notice of this hormone. Earlier studies sought connections between estrogen and mental skills with mixed results. One study of 800 women found that taking estrogen after menopause had no effect on later mental functions. Another showed that estrogen did not seem to protect intellectual function in general, although it did enhance verbal memory.

Nonetheless, the California study and others have provided enough evidence in favor of estrogen to spur much larger population studies of postmenopausal estrogen therapy and its possible preventive effect on Alzheimer's. A clinical trial of estrogen as a treatment in early-stage Alzheimer's disease is under way.

In the meantime, biochemical studies have come up with a string of related findings. Researchers have found that the cholinergic neurons of the brain have numerous estrogen receptors, and they occur on the same neurons that have receptors for nerve growth factor; that estrogen in animals boosts levels of nerve growth factor; and that estrogen injected in rats' brains strongly affects neurons in the cerebral cortex and the hippocampus--regions affected by Alzheimer's disease. These pieces of evidence have given rise to the hypothesis that nerve growth factor and estrogen interact in some way to protect cholinergic neurons from degenerating.

It is much too early, of course, to tell whether taking estrogen does reduce the risk of Alzheimer's disease. Like the other areas of treatment research, this one is still at a preliminary stage. And since estrogen replacement therapy following menopause is not recommended for all women, scientists have urged caution in interpreting the findings to date.

### **Calcium regulators.**

The theory that a rise in calcium levels in neurons is the final step in the biochemical pathway leading to Alzheimer's disease has raised more treatment possibilities. A drug that could keep this final step from taking place might prevent or help slow down the disease.

Drugs called calcium channel blockers, already in wide use to treat high blood pressure and other problems, might fill this role, say some researchers. Calcium enters and exits neurons through several kinds of channels, so finding the right channel and channel blocker may be a complex task. Currently one drug company is testing a channel blocker in Alzheimer's patients and other calcium regulators are being considered for trials.

### **Antioxidants.**

Still another theory about calcium imbalance points to out-of-control molecules known as oxygen

## Alzheimer's Disease

free radicals and the agents that disarm them, including antioxidants.

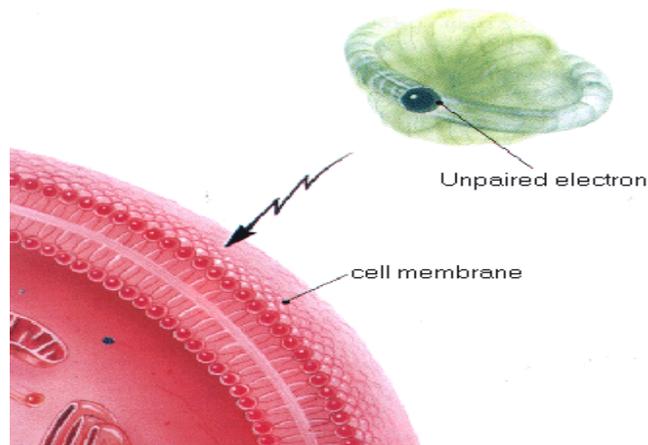
A free radical is a molecule with an unpaired electron in its outer shell. Ordinarily an oxygen molecule, like other molecules, has an even number of electrons in orbit. But the normal process of turning food into energy--metabolism--produces oxygen radicals with an odd number of electrons. The oxygen radical is extremely reactive; it will latch readily onto another molecule--a part of the membrane or a unit of DNA, for instance. When this happens, it can set off a chain reaction, releasing chemicals that can be harmful to the cell. Scientists theorize that damage from oxygen radicals plays a role in aging as well as in diseases ranging from glaucoma to cancer.

In Alzheimer's disease, free radicals are suspects for several reasons. They attack phospholipids, the molecules of fat in neuron membranes. Some researchers hypothesize that free radicals upset the delicate membrane machinery that regulates what goes into and out of a cell, such as calcium.

Free radicals may also have a connection with beta amyloid. One study has found that in neuritic plaques, beta amyloid breaks easily into fragments, releasing free radicals.

The body has certain lines of defense against oxygen free radicals. Enzymes like superoxide dismutase (SOD) and catalase can disarm the damaging oxygen molecules. And the vitamins in food known as antioxidants--vitamins C and E and beta-carotene, which is related to vitamin A--also counter free radicals.

Several proposed treatments for Alzheimer's hinge on the theory that free-radical damage plays a key role in the disease and that antioxidants, therefore, should be able to slow down its progression. One clinical trial is testing vitamin E and deprenyl, a drug that inhibits oxidation, to see if they can make a difference.



**Free Radicals: Shows an unpaired electron approaching a nerve cell membrane. This kind of oxygen molecule can set off a chain reaction that can harm neurons, perhaps playing a role in Alzheimer's disease.**

Another compound now in clinical trials, acetyl-L-carnitine, may also slow Alzheimer's by reducing the production of free radicals. This synthetic compound is very similar to a naturally occurring molecule that can help neurons carry out the process of metabolism. Acetyl-L-carnitine also may

provide important constituents for the synthesis of acetylcholine.

### **Anti-inflammatory drugs.**

Alzheimer's rates may be lower among people who take anti-inflammatory drugs than among those who do not. In a recent study of twins, one member of each pair had Alzheimer's and one did not. Many of the twins who did not have the disease had one thing in common: they took anti-inflammatory drugs for arthritis. A clinical trial is now testing whether the anti-inflammatory drug prednisone can slow the progress of the disease in its early stages.

## **Managing Symptoms**

In *The 36-Hour Day*, one of the first books on Alzheimer's from the caregiver's perspective, Nancy Mace and Peter Rabins devote several chapters to coping with the symptoms of Alzheimer's disease. "Some people fall when they first get out of bed," they write. "Have the person sit on the edge of the bed for a few minutes before walking."

These chapters are about daily routines and problems. "If all of the person's socks will go with all of his slacks, he doesn't have to decide which is right to wear with what... Many families have told us that a bath seat and a hand-held hose greatly reduce the bath time crisis."

When the first edition of this book came out in 1981, it filled a great void. Information on the symptoms of the disease was sparse and guidance on managing them even sketchier. Throughout the 1980's, other publications appeared, filled with informal observations about symptoms and coping strategies.

Toward the end of the decade, more and more formal research began to focus on this aspect of Alzheimer's disease. In contrast to the biological research described earlier, the low-tech, behavioral approach centers as much on family members and caregivers as on the patients themselves. The rationale is that if the people who care for Alzheimer's patients know how to cope with symptoms of the disease, they can reduce the degree of disability associated with it.

Current studies are looking at two kinds of caregiving strategies: those that help the patient maintain independence in daily activities as long as possible and those that help prevent disturbing behaviors.

### **Independence.**

Dressing, preparing simple meals, performing other household tasks: These are all things that many Alzheimer's patients can still do in the earlier stages of the disease. "If we go out," said Letty Tennis in her journal, "I still can fix my face and hair perfectly but I forget basic steps and go by a little piece of paper like do eyes, cheeks, lips, etc.... I never cook when alone...but I still can microwave."

Maintaining independence has obvious advantages: The longer the patient can function independently, the better his or her quality of life and self esteem. Strategies that increase or maintain independence as long as possible also lower the level of stress for the spouse, child, or

other caregiver.

Researchers are experimenting with several methods to slow the loss of independence. Some are looking for ways to improve cognitive functions. For instance, one research team has used mental stimulation exercises for 1 hour each day in an attempt to improve cognitive abilities. So far, the Alzheimer's patients who do these exercises show improvement in comparison with a control group. Moreover, the caregivers in the group who did the exercises reported lower stress levels. Researchers are now testing mental exercises in group settings outside the home.

Other studies are testing ways to improve patients' functional abilities. This term encompasses the ability to carry out the so-called activities of daily living (ADLs), such as dressing and eating, as well as the more complex instrumental activities of daily living (IADLs). The latter include tasks like shopping and cooking.

Some findings show promise. Techniques that have been successful in small studies of getting dressed include having the caregiver demonstrate what to do, so that the patient can mimic the action (the technical term is "modeling"). Another technique is laying out clothes in the order that they should be put on ("stimulus control"). Still another is "prompting." Verbal prompts are statements like, "Pick up the shirt. Put your arm in the sleeve." Physical prompts are when the caregiver uses touch to show the patient which arm to use.

Researchers are now extending these strategies to other activities, such as bathing and feeding. One of the most intriguing results of such studies is the effect that the strategies have had on other aspects of Alzheimer's disease. Improved functioning seems to go along with a significant improvement in the behavioral problems that afflict Alzheimer's patients and families.

### **Disturbing behaviors.**

In one of his journal entries, Cary Henderson commented: "I think this disease does make us kind of irrational--sometimes very irrational--and sometimes it's out of fear and sometimes it's being left out of things."

As Alzheimer's disease makes inroads into memory and mental skills, it also begins to alter emotions and behavior. An estimated 70 to 90 percent of Alzheimer's patients eventually develop behavioral symptoms. One of the most common is agitation, which Letty Tennis describes: "It's a feeling like no other--like your engine is racing 100 mph and you can't go anywhere.... I'm getting cross at people and I hate that. When my psychologist kept asking me questions--the same ones over and over, I got so impatient inside that I had a strange impulse to throw my purse on the floor or better yet to bite him and say NO MORE!"

In addition to agitation, Alzheimer's patients often experience feelings of anger, frustration, and depression. The disease can also lead to wandering, pacing, and screaming. Behavioral symptoms may become worse in the evening, a phenomenon called sundowning, or during certain daily routines, especially bathing. These symptoms of the disease and their effects on the family are thought to be one of the most common reasons that Alzheimer's patients are institutionalized.

### **Pharmaceuticals**

Drugs are one way to approach the behavioral symptoms of Alzheimer's disease. Most often prescribed are anti-psychotics or antidepressants, which were developed for use in psychiatry. They can have a tranquilizing effect, although physicians and caregivers report varying results with these drugs. Few scientific studies have tested their effectiveness specifically in Alzheimer's disease.

One area of special interest is the effect of antidepressants on cognitive function. Many antidepressants suppress activity in the neurons that use acetylcholine. These are the same neurons affected by Alzheimer's disease, so suppressed activity in these neurons might make the cognitive symptoms, such as loss of memory, even worse. Some studies show this may be true.

On the other hand, there is evidence that reducing depression may improve functional ability in people with Alzheimer's disease. In one study, for example, those patients who were more depressed were less able to carry out the activities of daily living than patients who were less depressed. The effects of depression on functioning appeared to be over and above the effects of cognitive impairment. This finding interests researchers because it raises the possibility that treating depression may be one way to improve functional abilities.

### **Behavior management**

The other approach to the behavioral side of Alzheimer's is itself behavioral. That is, it relies on behavior management techniques rather than drugs. Some behavior management techniques aim to influence the entire spectrum of disturbing behaviors. One study, for instance, is looking at the effects of bright lights and music on all behavioral symptoms. Another is testing a daily schedule of planned activities for patients and caregivers on the hypothesis that regular routines can alleviate many disturbing behaviors as well as reduce caregiver stress.

Other behavior management techniques have specific targets. Aggressiveness and agitation commonly afflict patients during bathing, for instance, so researchers are trying to pinpoint the precise circumstances or events that trigger the problem. They then will test methods of avoiding those triggers or alleviating the patient's distress in other ways.

Wandering and pacing are also common among Alzheimer's patients. One hypothesis suggests that if pacing and wandering can be accommodated in some way, both patients and caregivers will benefit. To test this idea, one researcher has arranged for Alzheimer's patients in a nursing home to have access to an outdoor sheltered park for pacing. In addition, the researchers have had stimulating patterns painted on the floors. The study will compare the effects of this approach to the effects of drugs and physical restraints, the more traditional ways to manage pacing and wandering.

Screaming, also common among Alzheimer's patients, may be affected by changes in the environment as well. Several researchers are testing the effects of music. One is experimenting with videotapes of the patient's relatives and direct social interaction, to see if they have an effect on screaming.

Studies of behavior management techniques fall into two groups. Many are still small descriptive studies. That is, their aims are to establish a base of knowledge about the disturbing behaviors, such as how prevalent they are and what circumstances trigger them.

Other studies are clinical trials of strategies that seem most promising. One current trial is comparing the effects of non-drug behavior management strategies to the effects of two different medications, haloperidol and trazodone, in treating disturbing behaviors.

## Caregiving

"You don't know when it's going to end or what to expect."

"Your friends...will say we think of you, or we'll visit, but they never do, because they don't know how to act around Alzheimer's."

"I must have looked at 30 different homes."

These quotes, culled from support groups and personal conversations, express a few of the special problems that confront the wives, husbands, children, and other family members who take care of Alzheimer's patients.

Formal research on caregiving, begun in the early 1980's, is still young. The early studies documented that caregiving has a severe impact on both the physical and mental health of the caregiver. Fatigue, insomnia, and other physical symptoms are frequent. Cardiovascular risk factors, such as high blood pressure, may be affected. Studies also have linked the high levels of stress in caregivers with depression, a sense of isolation, and strained relationships with other family members.

### Special Care Units for Alzheimer's Disease

Special care units or SCUs are separate areas for dementia patients in nursing homes, assisted living residences, and other caregiving facilities. They take different forms, but in general SCUs have special architectural features and/or programs tailored to the needs of dementia patients.

First appearing in the 1980's, SCUs have proliferated rapidly. About 9.6 percent of all U.S. nursing homes with 30 or more beds had SCUs by the end of 1990, according to the National Survey of Special Care Units in Nursing Homes. The number may continue to grow. A 1991/92 survey of Medicare/Medicaid nursing facilities found that between 13 and 14 percent of certified facilities had at least one SCU.

Aside from their dramatic growth, little is known about SCUs as a group. What features do they offer? Which features, if any, make a difference to patients, families, or staff? Ten research teams are now studying SCUs in search of answers to questions like these.

Early in these studies it became clear that SCUs vary widely. Some offer only one special feature, such as a sheltered area for pacing, perhaps, or staff training. Most have several special features, such as family counseling, support groups, and therapeutic activities for patients.

Still unknown is whether or not these special features make a difference. To find out, investigators

## Unraveling the Mystery

are studying both SCU patients and dementia patients in traditional care settings, comparing them in areas such as: mental function, frequency of disturbing behaviors, degree of family involvement with the patient, staff and family satisfaction with the SCU, and costs in relation to benefits.

The studies, begun in 1991, will be completed in 1996.

### **Who are family caregivers?**

Researchers have found that the greatest number of family caregivers are wives and husbands; daughters come next. Many caregivers are single women.

Researchers are now studying the experiences of caregivers from various ethnic and racial groups to see if their approaches to caregiving differ. African-American caregivers, according to several studies, are less likely to see caregiving as a burden and more likely to share it with a large number of extended family members, when compared to white caregivers. Scientists are exploring these differences to see if they can pinpoint the coping strategies or other factors that affect how different racial and ethnic groups perceive caregiving.

### **What can be done to reduce the burden?**

This is a critical research question. Scientists are testing various methods (known in the language of research as interventions) to help caregivers. These fall into three broad categories.

#### **Emotional support**

One major hypothesis is that social support can help reduce stress and other caregiving problems. Support groups, individual counseling, and family counseling all fall into this category, and they are being studied in various ways. For example, one study is comparing two different forms of social support--support groups and home visits from professionals--to see if one is more effective than the other in boosting caregiver well-being and reducing the sense of burden.

To date, studies have generally shown a high level of satisfaction with support groups, although it is not clear whether they also help decrease caregivers' sense of burden. Individual counseling has alleviated specific problems such as depression.

#### **Services**

Help from community groups or professionals is another promising way to ease the difficulties facing caregivers. Probably the most common service, and the most studied so far, is respite care. This is the broad term for a variety of situations in which someone else cares for the patient for a period of time, giving the principal family caregiver some temporary relief. Respite services are offered in the home, in day care facilities, and even in institutions where patients stay a limited time, usually a week or two. So far studies of respite care show a very modest benefit, and current research is looking for ways to increase its impact.

### **Knowledge and skills training**

Another active hypothesis is that Alzheimer's caregivers will benefit by learning more about the disease, including the resources available to them and specific skills for coping with its symptoms. Research projects, for instance, have trained caregivers in behavior management techniques and other ways to resolve day-to-day problems.

The outcomes of many of these studies are positive, in that caregiver behavior and sometimes patient behavior is changed. In some cases, these studies have also demonstrated improvements in caregiver stress, anxiety, and depression. On the other hand, some of these studies show that decreased stress does not necessarily translate into a reduced sense of burden.

A fourth category of interventions combines all three of these approaches. Studies of such comprehensive efforts suggest that the more components they have, the better the chance that they will meet the needs of caregivers. However, questions remain about the cost effectiveness of comprehensive interventions and about the relative benefits of their individual components.

### **Other approaches**

In the attempt to develop better interventions, researchers are now trying to find and sort out the many factors that determine caregiver stress. For instance, one study is looking at caregiver personality, the degree of care needed, and resources available to the caregiver. The study's goal is to see how these factors interact to influence the caregiver's sense of burden.

Studies are also exploring when and how Alzheimer's caregivers use formal services--adult day care or home health aides, for instance. So far, the findings suggest that most caregivers delay getting formal services until their situations are extremely stressful.

### **Institutional care**

While finding services to help with family care may be difficult, Alzheimer's families say that the decisions surrounding placement in a nursing home can be even harder. Whether and when to turn to a nursing home is the first and some say the most difficult decision. Then come decisions on what type of care is best for the patient and affordable for the family. An informal board and care facility, where patients are supervised in a home setting? An assisted living facility, where patients receive some help with the activities of daily living? Or a traditional nursing home? The options also include special care units within nursing homes and assisted living facilities.

Research is now focusing on various kinds of institutional care. For instance, one study is looking at 100 board and care homes and 100 of their residents to see what factors affect the care received in these facilities. Another study is focusing on nurses aides in one New York City nursing home in an attempt to understand how work situations affect their caregiving behavior. The overall aim is to identify strategies that can lead to improvements in the quality of care and lighten the burdens of caregiving.

## **Further Reading**

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## **Potential Biomedical Treatments**

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# **Part 2**

## **Diagnostic Criteria**

## Alzheimer's Disease

# Is it Alzheimer's disease?

## Primary care physicians' growing responsibility for diagnosis

Steven R. Gambert, MD

### PREVIEW

According to one estimate, Alzheimer's disease has been diagnosed in more than 4 million Americans. As our population continues to age, we can expect to see a sharp increase in this number. By the middle of the next century, there are projected to be almost as many Americans over age 80 as there now are over age 65. Primary care physicians are bound to see more and more patients who appear to have Alzheimer's disease, and the burden is on them to rule out other, treatable forms of dementia. Dr Gambert describes how to distinguish the true cognitive dysfunction of Alzheimer's disease and where to go from there.

Alzheimer's disease is classified as an age-prevalent disorder, although it appears to recognize no age boundary, with the youngest reported patient being only 28 years old. The disease is found in about 5% of people over age 65. In 1900, only 4% of the US population was over age 65. By 1980, this percentage had increased to 12%; by 2020, it is expected to reach 20%. The marked increase in people over age 80 is even more important, since Alzheimer's disease is found in 20% to 40% of people over age 80 and this age-group is the fastest-growing segment of our population.

Obviously, the "graying of America" will have a dramatic effect on age-prevalent disorders, and Alzheimer's disease has profound ramifications, not only on patients but also on families, caregivers, and society.

### Diagnostic requirements

Dementia is an impairment in cognitive function that is significant enough to interfere with the ability to conduct normal activities of daily living. It consists of impaired memory,

language ability, motor activities, recognition, and abstract thinking. Alzheimer's disease is the leading cause of dementia, accounting for 50% to 60% of all cases. It is characterized by gradual onset and progressive deterioration of cognitive function; there must be an absence of other causes for the dementia.

Alzheimer's disease was first described in 1907 by Alois Alzheimer, a pathologist who, using light microscopy, noted changes in the neurohistology of middle-aged persons who had cognitive decline. Plaques (>20/high-power field) and neurofibrillary tangles remain the hallmarks of this disorder, despite the many decades that have passed since Alzheimer's discovery. Other associated histologic features include cortical neuronal loss, loss of dendrites, neuronal atrophy, and granulovacuolar degeneration.

Since definitive diagnosis would require demonstration of the characteristic histologic features at autopsy, the diagnosis of Alzheimer's disease is made on clinical grounds after all other causes of dementia have been excluded.

## Severity and progression

Many patients have a family history of Alzheimer's disease, but even more do not. Clearly, people with a family history of the disease are at greater risk, assuming they live into late adulthood. However, the longer the elderly live without getting Alzheimer's disease, the better the chance of never getting it.

Persons under 65 with the characteristic clinical features are considered to have type 1 disease, or pre-senile dementia of the Alzheimer type; those over 65 have type 2 disease, or senile dementia of the Alzheimer type.

Dementia can be characterized as mild, moderate, or severe. In mild disease, work or social activities are impaired but the capacity for independent living remains. Dementia is considered moderate when independent living presents a hazard, and severe when cognition and function are so impaired that continuous supervision is required.

## Nursing home placement

Alzheimer's disease is the most common reason for nursing home placement. It seems logical that patients with the most severe dementia would most often require custodial care, but studies have found wide variability among what family caregivers can and cannot tolerate. The most difficult problem to manage is nighttime sleep disturbance. However, other problems that are often encountered with dementia, such as daytime wandering, incontinence, and falls, also eventually require nursing home placement, despite the family's best efforts to provide additional care in the home.

Patients and families who are able to pay for required services are in an enviable position to choose the type of care they desire and the location for the care, whether it be in the home, a day-care center, or a nursing home. However, costs are prohibitive for most

people. After the patient's personal assets have been exhausted, the family usually relies on governmental assistance for care costs.

Each state has different program requirements. For example, certain states offer a community-option program, whereby necessary services are delineated and costs are computed to determine what would be the most cost-effective location for care of a particular patient. Primary care physicians should become familiar with the requirements in their area and be willing to appeal rulings that may be economically worthwhile but not in the best interest of the patient and family.

## Direct and indirect costs

When lost income and the price of home care services are combined with the costs of nursing home care for patients with dementia (more than half of residents have dementia), it is easy to see why the total direct and indirect costs to American society each year exceed \$90 billion. And costs are not just economic; Alzheimer's disease has a major effect on the physical and psychological well-being of everyone concerned.

In addition, Alzheimer's disease has been reported to be the fourth leading cause of death in adult Americans (>100,000 per year). About 25% of Alzheimer's disease patients die malnourished, partly because they do not remember to eat but partly because disease-associated problems inhibit simple body functions (eg, apraxia limits the ability to swallow).

Bronchopneumonia is listed as the cause of death in more than half of patients with Alzheimer's disease. Other reported causes of death are cerebrovascular disease (in about 10%), cardiovascular disease (in 3.5%), and cancer (in 2.3%). These last two statistics seem curiously low, since most patients are elderly. These findings may imply that Alzheimer's disease has some "protective" role against cardiovascular disease and cancer.

## Diagnosis: Is it Alzheimer's Disease?

### Other causes of dementia

Primary care physicians have an important responsibility in ascertaining the exact cause of cognitive decline. Thus, an awareness of early warning signs of dementia and an ability to distinguish the myriad other causes from Alzheimer's disease are critical. Of the 40% to 50% of cases of dementia that are not related to Alzheimer's disease, about 25% are believed to be due to multiple infarcts resulting from embolic causes or small hemorrhages. There still remains a significant number of patients who have a potentially treatable cause of dementia, including things as varied as metabolic disorder, infection, and vitamin B12 deficiency. Since no confirmatory test is available, Alzheimer's disease remains a diagnosis of exclusion. Thus, the burden is on the physician to rule out other, treatable and even preventable forms of dementia or problems that resemble dementia. Use of the mnemonic DEMENTIA (see below) is helpful in remembering the following possible causes.

### Diagnostic criteria for dementia and Alzheimer's disease

#### Dementia

- A. Multiple cognitive deficits manifested by both 1 and 2
  - 1. Impaired short- or long-term memory
  - 2. One or more of the following cognitive disturbances:
    - a. Impaired language ability
    - b. Impaired ability to carry out motor activities
    - c. Impaired ability to recognize objects
    - d. Impaired abstract thinking (eg, planning, organizing)
- B. Deficits in A are sufficient to interfere with work or Social activities and represent a significant decline in function
- C. Deficits do not occur exclusively during the course of delirium

- Alzheimer's Disease Dementia as determined by A through C, plus
- D. Disease course is characterized by gradual onset and continuing cognitive decline
- E. Cognitive deficits are not caused by any of the following:
  - 1. Another progressive central nervous system disorder (eg, Parkinson's disease, Huntington's disease)
  - 2. A systemic condition (eg, hypothyroidism, niacin deficiency)
  - 3. A substance-induced condition
- F. Disturbance is not better accounted for by another disorder (eg, major depressive disorder, schizophrenia)

Adapted from the American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 4th ed. Washington, DC : Am Psychiatric Assn., 1994:142,43,51,52.

### Causes of dementia other than Alzheimer's disease

When assessing patients for possible Alzheimer's disease, other causes of dementia or features that resemble dementia can be recalled with use of the mnemonic DEMENTIA.

#### D Drug use

#### E Emotional disorders

#### M Metabolic disorder

#### E Eye and ear disorders

#### N Nutritional disorders and normal-pressure hydrocephalus

#### T Tumors and trauma Infection

#### A Atherosclerosis and alcoholism

#### Drug use

Perhaps the most common cause of reversible dementia is the use of certain drugs. Although oral preparations are most often implicated,

eye drops with beta-adrenergic or anticholinergic properties have also been reported to cause cognitive changes. Steroid therapy, especially in high doses, and anticholinergic drugs or agents with anticholinergic properties (eg, high-dose, low-potency psychotropic agents) are also prime suspects.

Physicians should ascertain what medications are being taken, including over-the-counter preparations, and ask that all drugs, in whatever form used, be brought to the next office visit.

### **Emotional disorders**

Emotional problems masquerading as dementia have been given the name "pseudodementia." Depression is the most common such problem affecting the elderly. History taking may provide the clues necessary to make a proper diagnosis, but at times, psychological testing or even a trial of antidepressant therapy may be necessary. In addition, depression may coexist with another cause of dementia, such as early Alzheimer's disease.

In general, dementia caused by depression usually has an abrupt onset and is self-limited. When questioned, patients often try to avoid answering, and when pressed for an answer, they provide "near-miss" responses. In contrast, patients with Alzheimer's disease try to respond but provide inappropriate answers.

In addition, somatic complaints are more common in persons with depression.

### **Metabolic disorders**

Among the many possible metabolic causes of cognitive change are hyperthyroidism, hypothyroidism, hyperglycemia, hypoglycemia, hypercortisolism, uremia, hepatic failure, and electrolyte abnormalities.

### **Eye and ear disorders**

A person with a disorder affecting the eyes or ears may give the false impression of having dementia when the only problem is an inability to hear or understand the question posed. Social isolation that sometimes results from these disorders may cause changes in the psychological state, but true dementia is not present.

### **Nutritional disorders and normal-pressure hydrocephalus**

Nutritional disorders, particularly vitamin B12 deficiency, may alter cognition. In the United States, the lower limit of normal for vitamin B12 levels is considered to be 200 pg/mL. However, data suggest that patients with dementia and a level less than 300 pg/mL should be given a trial of vitamin B<sub>12</sub> therapy. Because of the reversibility of certain neurologic problems at the low range, the lower limit of normal is set higher than 200 pg/ml in some other countries.

Folate deficiency has been implicated as a possible cause of dementia, and even though its role is still being debated, it should be ruled out. Animal studies suggest that significant protein malnutrition may also be a cause of cognitive decline.

Normal-pressure hydrocephalus can result in dementia, which may be completely reversed with early intervention. Unfortunately, most cases are discovered late, when little change can be expected.

### **Tumors and trauma**

Tumors and trauma involving the central nervous system should be ruled out with thorough history taking and physical examination and use of computed tomography.

### **Infection**

Infection of the central nervous system (eg, tertiary syphilis, Lyme disease) can lead to dementia.

### **Atherosclerosis and alcoholism**

Atherosclerosis may cause multiple infarcts; when a critical amount of brain matter is lost through this process, irreversible dementia results. This process, like embolic events, tends to follow a "stuttering" or stepwise progression and often causes additional neurologic findings. A history of hypertension is common in patients with this cause of dementia. In contrast to patients with Alzheimer's disease, who are predominantly women over 70, these patients tend to be men in their 50s and 60s.

Alcoholism can affect the cognitive state, not only by its damage to hepatic function and nutritional condition but also by direct toxic effects on the brain. Alcoholism is usually not considered in elderly patients unless a lifelong problem has been noted. Increasingly, however, it is being seen as an issue among older people and so should be considered. The highest rate of new alcoholism is reported to be among elderly men who have lost their wives. They often avoid early recognition because drinking takes place at home and while alone.

### **Cognitive screening in older patients**

Unfortunately, many people still believe that cognitive decline is to be expected as part of growing old, and they may fail to mention problems until late in the disease course. Therefore, primary care physicians should include some form of cognitive screening in periodic examination. This establishes a baseline for comparison with later examinations and, hopefully, a means of detecting any changes early. In addition, family members should be encouraged to seek medical advice for any changes they see in their elderly relatives rather than waiting until some classic sign or symptom develops.

More often than not, presentation in elderly patients is nonspecific, and cognitive changes

may be an early manifestation of many conditions that are not related to normal aging or Alzheimer's disease. For example, although normal aging does bring some changes in short-term memory, they are not significant enough to interfere with activities of daily liv-

**Alcoholism changes cognition by direct toxic effects on the brain. The highest rate of new alcoholism is reported to be among elderly men who have lost their wives.**

ing. Furthermore, the normal aging process should never affect long-term memory.

Another common source of confusion is the difference between a reduced attention span and true memory loss. Many patients are inappropriately diagnosed as having dementia when they simply lack the ability to pay attention, perhaps because of preoccupation with some psychological problem or medical condition. Obviously, patients without an appropriate attention span find it impossible to remember what was said, but a reduced attention span does not constitute memory loss.

Primary care physicians can help assess cognitive function with use of a formal test, such as the Mini-Mental State Examination (Table 1).

### **Support for the patient and family**

When careful evaluation, including appropriate laboratory and diagnostic testing, firmly indicates that Alzheimer's disease is the correct diagnosis, the important next step is to meet with the patient and all concerned family members. Primary care physicians are a valuable resource in preparing the family and caregivers for the challenges ahead and should describe the problem, delineate what to expect, and provide literature and information. Referral to a local chapter of the Alzheimer's Association is advised, and legal and ethical considerations (eg, advance directives, living

wills should be discussed.

Symptoms that may further inhibit home care should be addressed and caregivers instructed to report any new problem. For example, urinary incontinence may be the result of an uninhibited neurogenic bladder from Alzheimer's disease. However, as in other patients, it can also be due to urinary tract infection or other cause and thus be amenable to treatment. Behavior problems should be dealt with using a variety of nonpharmacologic and pharmacologic methods to prevent frustration and eventual burnout among family members and caregivers. As with many other problems affecting the elderly, a team approach utilizing the primary care physician and other skilled professionals is often the most beneficial and effective in maintaining the highest quality of life possible for both patients and family.

### Summary

Alzheimer's disease promises to be one of our greatest public health priorities in the next century. Although new methods of diagnosis and treatment appear on the horizon, the

disease currently remains difficult to confirm and lacking a cure. Primary care physicians can be a vital resource and patient advocate by keeping abreast of advances and the rapidly changing literature dealing with the disease. The articles that follow in this symposium summarize the latest findings on therapy for Alzheimer's disease and address specific issues regarding the disease's effects on cognition, behavior, and family interaction.

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## Diagnosis: Is it Alzheimer's Disease?

Table 1: Minimental State Examination

<u>Task</u>	<u>Instructions</u>	<u>Scoring</u>
Date orientation	“Tell me the date”. Ask for omitted items.	One point each for year, season, date, day of week, and month.
Place orientation	“Where are you?” Ask for omitted items.	One point each for state, county, town, building, and floor or room.
Register three objects	Name three objects slowly and clearly. Ask the patient to repeat them.	One point for each item correctly repeated.
Serial sevens	Ask the patient to count backwards from 100 by 7. Stop after five answers. (Or ask to spell “world” backward).	One point for each correct answer.
Recall three objects	Ask the patient to recall the objects mentioned above.	One point for each item correctly remembered.
Naming	Point to your watch and ask the patient, “What is this?” Repeat with a pencil.	One point for each correct answer.
Repeating a phrase	Ask the patient to say, “No ifs, ands, or buts.”	One point if successful on first try.
Verbal commands	Give the patient a plain piece of paper and say, “Take this paper in your right hand, fold it in half, and put it on the floor.”	One point for each correct action.
Written commands	Show the patient a piece of paper with “close your eyes” printed on it.	One point if the patients eyes close.
Writing	Ask the patient to write a sentence.	One point if the sentence has a subject and a verb and makes sense.
Drawing	Ask the patient to copy a pair of intersecting pentagons onto a piece of paper.	One point if the figure has ten corners and two intersecting lines.

\*A score of 24 or more considered normal. Adapted from Folstein, MF, Folstein SE, McHugh FR. “MiniMental State”; a practical method for grading the cognitive state of patients for the clinician. J. Psych Res. 1975; 12(3): 189-96.

## Alzheimer's Disease

# Diagnosis and Treatment of Alzheimer Disease and Related Disorders

Consensus Statement of the American Association for Geriatric Psychiatry, the Alzheimer's Association, and the American Geriatrics Society

Gary W. Small, MD; Peter V. Rabins, MD; Patricia P. Barry, MD; Nell S. Buckholtz, PhD; Steven T. DeKosky, MD; Steven H. Ferris, PhD; Sanford I. Finkel, MD; Lisa P. Gwyther, MSW; Zaven S. Khachaturian, PhD; Barry D. Lebowitz, PhD; Thomas D. McRae, MD; John C. Morris, MD; Frances Oakley, OTR; Lon S. Schneider, MD; Joel E. Streim, MD; Trey Sunderland, MD; Linda A. Teri, PhD; Larry E. Tune, MD

**Objective.**--A consensus conference on the diagnosis and treatment of Alzheimer disease (AD) and related disorders was organized by the American Association for Geriatric Psychiatry, the Alzheimer's Association, and the American Geriatrics Society on January 4 and 5, 1997. The target audience was primary care physicians, and the following questions were addressed: (1) How prevalent is AD and what are its risk factors? What is its impact on society? (2) What are the different forms of dementia and how can they be recognized? (3) What constitutes safe and effective treatment for AD? What are the indications and contraindications for specific treatments? (4) What management strategies are available to the primary care practitioner? (5) What are the available medical specialty and community resources? (6) What are the important policy issues and how can policymakers improve access to care for dementia patients? (7) What are the most promising questions for future research?

**Participants.**--Consensus panel members and expert presenters were drawn from psychiatry, neurology, geriatrics, primary care, psychology, nursing, social work, occupational therapy, epidemiology, and public health and policy.

**Evidence.**--The expert presenters summarized data from the world scientific literature on the questions posed to the panel.

**Consensus Process.**--The panelists listened to the experts' presentations, reviewed their background papers, and then provided responses to the questions based on these materials. The panel chairs prepared the initial drafts of the consensus statement, and these drafts were read by all panelists and edited until consensus was reached.

**Conclusions.**--Alzheimer disease is the most common disorder causing cognitive decline in old age and exacts a substantial cost on society. Although the diagnosis of AD is often missed or delayed, it is primarily one of inclusion, not exclusion, and usually can be made using standardized clinical criteria. Most cases can be diagnosed and managed in primary care settings, yet some patients with atypical presentations, severe impairment, or complex comorbidity benefit from specialist referral. Alzheimer disease is progressive and irreversible, but pharmacologic therapies for cognitive impairment and nonpharmacologic and pharmacologic treatments for the behavioral problems associated with dementia can enhance quality of life. Psychotherapeutic intervention with family members is often indicated, as nearly half of all caregivers become depressed. Health care delivery to these patients is fragmented and inadequate, and changes in disease management models are adding stresses to the system. New approaches are needed to ensure patients' access to essential resources, and future research should aim to improve diagnostic and therapeutic effectiveness.

ALZHEIMER DISEASE (AD), the most common of the dementing disorders, affects an estimated 4 million people in the United States.<sup>1,2</sup> It causes anguish to caregivers and family members, who must cope with their loved one's steady and irreversible decline in cognition, functioning, and behavior. Patients and caregivers often mistake early symptoms for normal aging changes, and physicians may fail to recognize the initial signs of dementia or misdiagnose them, perpetuating myths and fallacies about the disease in particular, that the early signs of dementia are "just old age" or "just senility." Alzheimer disease and aging, however, are not synonymous. Expected cognitive changes of aging--for example, a slow-hug of information processing--are benign, while dementia is progressive and disabling, not an inherent part of growing old.

A complete list of author affiliations and financial disclosures appears at the end of this article. Reprints: Gary W. Small, MD, University of California at Los Angeles, Neuropsychiatric Institute and Hospital, 760 Westwood Plaza, Room 37-432, Los Angeles, CA 90024-1759.

Recent progress in understanding the diagnosis and treatment of AD and related disorders has

benefited many patients. Early and accurate diagnosis may prevent the use of costly medical resources and allow patients and family members time to prepare for future medical, financial, and legal challenges. While no current therapy can reverse the progressive cognitive decline, several pharmacologic agents and psychosocial techniques have been shown to provide relief for the depression, psychosis, and agitation often associated with dementia, and pharmacotherapy may produce cognitive improvement in many patients. Yet, some primary care physicians, who are the port of entry for most patients with early-stage dementia, remain uninformed and thus unable to diagnose, treat, and manage these patients effectively. As the number of older Americans grows, so will the magnitude of the problem. Some epidemiologists project the number of patients with AD to reach 14 million by 2040.<sup>2</sup>

For these reasons, on January 4 and 5, 1997, the American Association for Geriatric Psychiatry, the Alzheimer's Association, and the American Geriatrics Society convened a Consensus Conference on the Diagnosis and Treatment of Alzheimer Disease and Related Disorders. After a day of presentations by experts in the relevant fields and discussion with the audience, a consensus panel, chaired by Gary W. Small, MD, and Peter V. Rabins, MD, and comprising experts from psychiatry, neurology, geriatrics, primary care, psychology, nursing, social work, occupational therapy, epidemiology, and public health and policy, considered the scientific evidence--including 3 recently prepared consensus documents on the diagnosis, evaluation, and treatment of AD and dementia? The panel formulated a consensus statement directed at primary care practitioners to address the following questions:

- How prevalent is AD and what are its risk factors?
- What is its impact on society?
- What are the different forms of dementia and how can they be recognized?
- What constitutes safe and effective treatment for AD?
- What are the indications and contraindications for specific treatments?
- What management strategies are available to the primary care practitioner?
- What are the available medical specialty and community resources?
- What are the important policy issues and how can policymakers improve access to care for dementia patients?
- What are the most promising questions for future research?

### **HOW PREVALENT IS AD AND WHAT ARE ITS RISK FACTORS? WHAT IS ITS IMPACT ON SOCIETY?**

Alzheimer disease begins most frequently in late life, generally after the age of 60 years, although in rare cases the disorder may begin as early as age 30 years. Disease progression is gradual and continuous, and the average patient may expect to live from 8 to 10 years after symptom onset. The reported prevalence of AD varies according to the age ranges of sampled populations, dementia definitions, and assessment methods? Approximately 6% to 8% of all persons older than 65 years have AD,<sup>19</sup> and the prevalence of the disease doubles every 5 years after the age of 60 years, so that nearly 30% of the population older than 85 years has AD.

Greater awareness of the prevalence of AD might prompt earlier physician recognition and intervention. One study found that only 40% of primary care physicians knew that AD is the most common cause of dementia in older persons.<sup>13</sup> Furthermore, community-wide prevalence surveys detect many undiagnosed cases. Research has shown that physicians often fail to correctly apply a diagnosis of dementia, making a positive diagnosis when the disease is not present or failing to recognize it when it is? Investigators attribute these errors to a lack of attention to cognitive

functioning in routine medical examinations and to misperceptions about the normal aging process?<sup>19-22</sup> Given the large number of older Americans likely to become cognitively impaired, primary care physicians require more effective strategies to recognize the disease's early signs and symptoms.

The primary risk factors for AD are age and family history. Some studies suggest that by the age of 90 years, almost 50% of persons with a first-degree relative with AD develop the disease themselves?<sup>23,24</sup> Genetic mutations on chromosomes 1, 14, and 21 cause rare, early-onset familial forms,<sup>25-27</sup> and the apolipoprotein E-4 (*APOE-4*) allele on chromosome 19 is associated with an increased risk for the common late-onset AD? However, the *APOE-4* allele also is found in elderly persons without AD and is not present in many patients with the disease. Genetic testing for *APOE* is not recommended for predictive screening in asymptomatic persons, and experts disagree on its usefulness as a diagnostic test for AD in demented patients?<sup>29,30</sup> Some forms of late-onset AD also have been linked to chromosome 12.<sup>31</sup> Other possible risk factors for AD include additional, but as yet undefined, susceptibility genes, a previous head injury, female sex, and lower education level. Possible, but not proven, protective factors include the use of estrogen replacement therapy and nonsteroidal anti-inflammatory drugs.

Alzheimer disease exacts a major toll on society. When the costs of medical and long-term care, home care, and lost productivity for caregivers are totaled, the direct dollar expenditure and indirect costs (ie, resource loss, family care) approach \$100 billion each year.<sup>32,33</sup> Medicare, Medicaid, and private insurance bear much of the direct cost, but families who care for patients with AD assume the largest portion of expenses.

The financial costs of AD provide an incomplete picture of the total burden. The emotional toll on patients and their families is profound and a significant source of caregiver morbidity. Indeed, up to 50% of primary caregivers of AD patients develop significant psychological distress? Thus, any economic assessment actually underestimates the true cost of the disease to society unless quality of life of both patients and caregivers is included in the analysis?

### **WHAT ARE THE DIFFERENT FORMS OF DEMENTIA AND HOW CAN THEY BE RECOGNIZED?**

Recent guidelines have been published on the diagnosis and assessment of dementia.<sup>4</sup> Dementia is an acquired syndrome of decline in memory and other cognitive functions sufficient to affect daily life in an alert patient? Alzheimer disease is the most common form of dementia, accounting for two thirds or more of all dementia cases, while vascular dementia accounts for approximately 15% of all dementias? The recently identified dementia associated with Lewy bodies (DLB) is receiving increased attention. A positive diagnosis of DLB requires both a finding of dementia and at least 1 of 3 core symptoms: detailed visual hallucinations, parkinsonian signs, and alterations of alertness or attention. Autopsy series suggest about 25% of dementias are DLB,<sup>37</sup> although DLB may overlap with AD and the dementia associated with Parkinson disease.

Alzheimer disease is characterized by gradual onset and progressive decline in cognition with sparing of motor and sensory functions until later stages. The average course of AD is approximately a decade, with a range of 3 to 20 years' duration from diagnosis to death, but the rate of progression is variable. Memory impairment is present in the earliest stages of the disease; patients have difficulty learning new information and retaining it for more than a few minutes. As the disease advances, the ability to learn is increasingly compromised, and access to older, more distant memories is lost. Other cognitive losses include aphasia, apraxia, disorientation, visuospatial dysfunction, and impaired judgment and executive functioning.

Cognitive impairment may affect daily life in several ways: patients have difficulty planning

## Alzheimer's Disease

meals, managing finances or medications, using a telephone, and driving without getting lost. These functional impairments may be the patient's or family's first sign that something is amiss. Many capacities remain intact in patients with mild to moderate AD, including the performance of self-care activities of daily living, such as eating, bathing, and grooming. Social skills often are intact until later stages of the disease.

Significant changes in behavior and mood often occur? Patients may evidence personality alterations, irritability, anxiety, or depression early in the disease process. Delusions, hallucinations, aggression, and wandering often develop in middle and late stages. Such behaviors are the most troubling to care-givers and frequently lead to family distress and nursing home placement?

The presence of either delirium or depression may confound dementia recognition. Delirium is a syndrome of acquired impairment of attention, alertness, and perception? Like dementia, delirium is characterized by global cognitive impairment; however, it can be distinguished by its acute onset, marked fluctuations in cognitive impairment over the course of a day, disruptions in consciousness and attention, and alterations in the sleep cycle. Hallucinations and visual illusions are common. A general medical condition, such as infection or metabolic disturbance, or pharmacologic toxicity typically causes delirium. Delirium and dementia often coexist, particularly in a hospital setting? Dementia is a risk factor for delirium and contributes to the higher prevalence of delirium in the elderly.<sup>40,41</sup> Thus, an episode of delirium in an older person should prompt a dementia evaluation when the delirium clears, if the cognitive impairment persists.

Depression and dementia may be mistaken for each other, and their differentiation presents a diagnostic challenge. Patients with AD often present with depressive symptoms. Such patients often minimize their cognitive deficits, while the patient with primary depression often shows impaired motivation during the cognitive examination and has cognitive complaints that exceed objectively measured cognitive deficits. Language and motor skills usually remain intact in patients with depression but often are impaired in AD. Nearly 50% of elderly patients with reversible dementia and depression will develop irreversible dementia within 5 years?

The diagnosis of AD must be primarily one of inclusion, not exclusion, as is often supposed. In approximately 90% of cases, the diagnosis can be made on the basis of a general medical and psychiatric evaluation?<sup>44</sup> Primary care physicians must be alert to early symptoms of AD and recognize that many patients seek out medical treatment for a reason other than cognitive difficulty. Any patient or family concerns about cognitive decline should trigger a mental status assessment and possibly a dementia evaluation.

The most important diagnostic tools are the informant interview and office-based clinical assessment. Physicians should interview both the patient and a reliable informant and inquire into the patient's current condition, medical and medication history, patterns of alcohol use, and living arrangements. The Functional Activities Questionnaire<sup>45</sup> and the Revised Memory and Behavior Problems checklist<sup>46</sup> are 2 useful informant-based instruments among several that help determine lapses in memory and language use, the ability to learn and retain new information, handle complex tasks, demonstrate sound judgment, and show usual behavior. Reported changes should be compared with the patient's past performance, as evidence of decline from previous functioning and impairment in multiple cognitive domains confirms the diagnosis.

Physicians should conduct a comprehensive physical examination, including a brief neurological and mental status evaluation. Also recommended are a brief quantified screen of cognitive function such as the Mini-Mental State Examination (MMSE),<sup>47</sup> and a laboratory evaluation, generally including a complete blood cell count, blood chemistries, liver function tests, a serological test for syphilis, and determination of thyroid-stimulating hormone and vitamin B<sub>12</sub> levels.<sup>3-5</sup> Other laboratory tests should be ordered if suggested by history or physical examination. Imaging studies

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are optional but recommended by many clinicians and experts. Noncontrast computed tomographic (CT) head scans are adequate in most instances. Some clinicians recommend magnetic resonance imaging (MRI) if vascular dementia is suspected, but white-matter changes revealed by T<sub>2</sub>-weighted MRI images generally are not related to dementia and should not be overinterpreted. If the diagnosis remains unclear, a repeat assessment in 6 months is indicated to check for progressive decline. Functional imaging studies, such as single-photon emission CT and positron emission tomography, may show the characteristic parietal and temporal deficits in AD or the widespread irregular deficits in vascular dementia.<sup>48,49</sup>

Patients with high educational levels may show normal cognitive function scores on tests such as the MMSE. Conversely, some elderly patients may have low MMSE scores and no decline in function, particularly those with lower educational levels. In clinical practice, cognitive measures are most useful as a quantitative baseline against which to compare future assessments. When the diagnosis is unclear, neuropsychological testing may distinguish between normal aging and dementia, as well as identify • deficits that point to a specific diagnosis. Recent changes in medical practice may hinder detection of AD. In today's managed care environment, many primary care physicians have limited time available for a comprehensive informant interview. To help expedite the process, it may be advantageous for nurses to interview patients or family members before they see the physician or use questionnaires that can be completed while they are waiting for the appointment. Telephone interviews are another option. Over reliance on and overinterpretation of laboratory findings, particularly CT and MRI results, should be avoided. The diagnosis of dementia usually is a clinical diagnosis. The laboratory assessment is performed to identify uncommon treatable causes and common treatable comorbid conditions.

Physical illness is common in patients with AD, but it rarely is the proximate cause of dementia. Vascular dementia is probably overdiagnosed?<sup>50</sup> Physicians should be suspicious of a history of "small strokes," unless they are accompanied by a clear demonstration of focal signs of motor or sensory impairment. A majority of dementia patients diagnosed as having vascular dementia are found on autopsy to have AD. However, cerebrovascular disease may contribute to the severity of cognitive symptoms of AD.<sup>51</sup> Potentially reversible dementias are uncommon.<sup>52</sup>

During the early stage of AD, the motor sensory, and cerebellar portions of • the neurological examination usually are normal. Focal motor or sensory signs, except fluent aphasia and apraxia, suggest vascular dementia or mixed vascular dementia and AD. Parkinsonian signs, especially the presence of "pill rolling" tremor in the years predating cognitive impairment, usually are indicative of Parkinson disease, not AD. Parkinsonian rigidity and bradykinesia accompanying the onset of dementia suggest DLB? Patients who present with an unusual onset or symptomology or whose neurological findings are atypical usually should be referred to a neurologist, geriatric psychiatrist, or geriatrician.

### **WHAT CONSTITUTES SAFE AND EFFECTIVE TREATMENT FOR AD? WHAT ARE THE INDICATIONS AND CONTRAINDICATIONS FOR SPECIFIC TREATMENTS?**

The primary goals of treatment of patients with AD are to improve quality of life and maximize functional performance by enhancing cognition, mood, and behavior. Treatments include pharmacologic and nonpharmacologic approaches, and the latter should be emphasized. Pharmacologic treatment should be introduced only if nonpharmacologic interventions prove ineffective, there is a significant risk of danger, or the patient is very distressed.

Several factors influence medication prescription for most older patients with AD, although there is considerable variability and need to individualize treatments. First, the elderly have decreased renal clearance and slowed hepatic metabolism. Second, elderly patients often take multiple

medications, so the clinician must be aware of potential drug interactions and adverse effects. Anticholinergic adverse effects pose a particular problem in persons with AD, as they can worsen cognitive impairment and may even cause delirium. Drugs causing central nervous system sedation may also worsen cognition. Third, elderly patients have decreased vascular tone and are subject to orthostasis, leading to falls. Thus, low starting doses and small increases should be used, and the periods between drug changes should be extended. Using the lowest effective dose can minimize adverse reactions, although dosing at subtherapeutic levels can be a problem. Nonessential polypharmacy should be avoided.

Before beginning treatment, it is recommended that physicians conduct a thorough medical examination and treat underlying medical conditions that can impair cognition (eg, thyroid disease). The continued use of any drug must be assessed and justified regularly over time.

### **Cognitive and Functional Enhancers**

**Cholinesterase Inhibitors.**--Improving central cholinergic neurotransmission is the only treatment currently available for the cognitive impairment of AD. Tacrine and donepezil, the 2 agents with labeling for treatments of AD approved by the US Food and Drug Administration, may improve cognitive functioning or delay decline and may also enhance clinician and family assessments and activities of daily living in patients with mild to moderate AD?<sup>53,54</sup> Open-label studies suggest beneficial effects on behavioral symptoms in some patients,<sup>55</sup> and prolonged cholinergic therapy may delay nursing home placement? The effects on patients with more severe disease or with other dementing disorders have not yet been assessed. Serial ratings of cognition (eg, MMSE) and functional status may be useful in monitoring drug effectiveness. Controlled data are lacking that dictate length of treatment, but short-term trials show that cognitive function returns to levels of placebo-treated patients when treatment with cholinesterase inhibitors is discontinued.

Tacrine is a centrally active aminoacridine with reversible nonspecific cholinesterase inhibitor activity and a duration of action of less than 7 hours. In clinical trials involving approximately 2000 patients with mild to moderate AD, between 20% and 30% of tacrine patients showed clinically observable improvement compared with placebo, representing on average about 6 months of deterioration? However, approximately one fifth experienced cholinergic adverse effects, most frequently gastrointestinal distress.<sup>58,59</sup> In addition, 29% had reversible elevations of serum transaminase levels 3 times above normal. After rechallenge, nearly 90% of patients can tolerate the compound? The starting dose for tacrine is 10 mg 4 times daily, which can be increased up to a maximum dose of 40 mg 4 times daily. Patients receiving tacrine should have a baseline and multiple follow-up alanine aminotransferase determinations.

Donepezil is a second-generation cholinesterase inhibitor that, like tacrine, shows dose-dependent activity but has a longer duration of inhibitory action and greater specificity for brain tissue. In 3 double-blind, placebo-controlled trials including more than 1000 patients, donepezil produced significantly greater cognitive effects (eg, enhanced memory, orientation, language, and reasoning) than placebo over periods of 12 and 24 weeks but did not cause hepatotoxicity?<sup>54,60</sup> The drug has a recommended starting dose of 5 mg/d, which may be increased to 10 mg/d after 1 month. The higher dose, while more efficacious, has a greater tendency to cause cholinergic adverse effects (eg, nausea, diarrhea, and insomnia) if increased too rapidly, and such effects may worsen behavior. Physicians may consider a trial of either of these agents for patients with mild to moderate AD. Many specialists believe that donepezil might prove advantageous as first-line therapy because it is given once a day and does not require a long introductory period and regular monitoring of liver function. Other cholinesterase inhibitors and cholinergic agonists are in clinical development and may become available in the near future.

**Other Agents.**-- Clinical trials of other agents to improve cognitive function are ongoing. These include estrogen, nonsteroidal anti-inflammatory agents, and botanical agents, such as ginkgo biloba. A study of 341 moderately impaired patients found that treatment with vitamin E ( $\alpha$ -tocopherol) or the selective monoamine oxidase-B inhibitor selegiline (with labeling indications being for treatment of Parkinson disease) showed decreased rates of functional decline compared with placebo treatment but no evidence of improvement? The evidence of clinical benefit for any of these agents is inconclusive at this time. As over-the-counter products are popular, physicians are encouraged to ask about their use.

### **Nonpharmacologic Cognitive Enhancement Strategies: Cognition-Oriented Psychotherapy**

Psychotherapeutic techniques proposed to restore cognitive dysfunction include reality orientation and memory retraining. They may yield some transient benefit,<sup>62</sup> but also may provoke frustration and depression in patients and caregivers. As the cognitive improvements associated with reality orientation and memory retraining are weak, many specialists believe the potential risks outweigh the benefits.

### **Treatment of Depression in Dementia**

**Pharmacotherapy.**--Patients with AD and depressive symptoms (eg, depressed mood, appetite loss, insomnia, fatigue, irritability, and agitation) should be considered for pharmacotherapy, even if they fail to meet the criteria for a depressive syndrome. The physician should carefully evaluate for indexes of major depression; suicidal ideation may indicate the need for intensive monitoring or hospitalization.

The choice of an antidepressant agent should be based on the drug's profile of adverse effects and the patient's general medical and psychiatric status. Many specialists favor the selective serotonin re-uptake inhibitors (SSRIs) fluoxetine, paroxetine, and sertraline as first-line treatment because they have fewer adverse effects than other antidepressants. Tricyclic antidepressants are effective drugs for depression, but these agents, especially amitriptyline, imipramine, nortriptyline, and clomipramine, have significant anticholinergic activity, can cause orthostatic hypotension and delayed cardiac conduction, and are risky in overdose. Nortriptyline, desipramine, bupropion, trazodone, and nefazodone are alternatives.

Monoamine oxidase inhibitors (MAOIs), including tranylcypromine and phenelzine, can cause postural hypotension and have complex drug interactions with sympathomimetic agents, narcotics such as meperidine, and serotonergic agents. The MAOIs also require dietary modifications. These agents should be considered only for patients who are un-responsive to or unable to tolerate other antidepressant medications. If they are used, adequate supervision should be arranged.

**Nonpharmacologic Strategies.**--A comprehensive system of humane care for patients with dementia requires consideration of psychosocial strategies to enhance quality of life. These include emotion-oriented psychotherapy, such as "pleasant events" and "reminiscence" therapy,<sup>2-4</sup> and stimulation-oriented treatment, including art and other expressive recreational or social therapies, exercise, and dance. Support groups for patients with mild impairment also may provide a constructive environment to help mobilize cognitive and behavioral resources. Despite a paucity of well-controlled data, preliminary studies and clinical practice suggest that these interventions may decrease behavioral problems and improve mood in patients and family alike?<sup>66-68</sup>

## Treatment of Agitation and Psychosis in Dementia

Agitation is a general term that refers to a range of behavioral disturbances, including aggression, combativeness, shouting, hyperactivity, and disinhibition. As many as 50% of all dementia patients exhibit agitation, particularly in middle and later stages of the illness? Psychosis (paranoia, delusions, and hallucinations) is far less frequent but can cause distress to patients and lead to violence. These symptoms can overlap, may be difficult to distinguish, and are among the most common causes of institutionalization or specialist referral.

Undiagnosed medical problems, pain, depression, anxiety, loss of sleep, or delirium may cause agitation. Unaddressed interpersonal or emotional issues, such as fear of abandonment, also may lie at the root of the disturbance. Treatment of underlying medical conditions, reassurance, attention to the environment, or emotion-oriented psychotherapy may reduce agitation.

A meta-analysis of published studies demonstrates that antipsychotic drugs can produce a modest improvement in some behavioral symptoms in dementia<sup>70</sup> and may be most effective for psychotic symptoms.<sup>71</sup> These agents are the only pharmacologic treatments available to treat psychotic symptoms, and they are widely used in the treatment of agitation. Newer drugs, such as the atypical antipsychotics clozapine, risperidone, and olanzapine, have not been well studied in the elderly patient with dementia, but mounting clinical evidence supports their use. Anecdotal evidence suggests risperidone and clozapine are effective at very low doses in the treatment of agitation and psychosis in elderly patients?<sup>72,73</sup> In patients with Parkinson disease, clozapine avoids the extrapyramidal effects of conventional antipsychotics,<sup>73,74</sup> and risperidone's effectiveness at low doses also may limit its extrapyramidal adverse effects? Other new atypical antipsychotics, including sertindole, quetiapine, and ziprazodone, may soon become available.

Clinical trial data indicate comparable efficacies among antipsychotic drugs; therefore, clinicians should base their choice of specific agents on their profile of adverse effects. Common adverse events associated with high-potency compounds (eg, haloperidol) include parkinsonian symptoms; with low-potency agents (eg, chlorpromazine), sedation, postural hypotension, and anticholinergic effects. Less frequent, but more serious, adverse effects are tardive dyskinesia and neuroleptic malignant syndrome, which have been reported with conventional antipsychotics and risperidone, but not clozapine.<sup>75</sup> However, clozapine can produce anticholinergic effects and carries a risk of agranulocytosis, requiring blood-count monitoring. Development of non-life-threatening adverse effects should first be treated by dose reduction. Referral to a specialist is helpful when withdrawing patients from antipsychotic drugs.

Benzodiazepines also have been used in the treatment of behavioral disorders associated with dementia. While helpful for treating anxiety or infrequent agitation, they appear less effective than antipsychotics for more severe symptoms. The most frequently reported adverse effects of benzodiazepines include sedation, ataxia, amnesia, confusion, and disinhibition. Such short-acting benzodiazepines as oxazepam and lorazepam are preferred over long-acting drugs (eg, diazepam, chlorthalidopoxide, and flurazepam) because the latter drugs and their metabolites accumulate in the blood and are more likely to cause adverse effects?<sup>6</sup> Given such risks, the use of benzodiazepines should be minimized.

Other agents explored in the treatment of behavioral disorders in dementia include the anticonvulsants carbamazepine<sup>77</sup> and valproate,<sup>78</sup> the 5-hydroxytryptophan modulator trazodone,<sup>79</sup> buspirone,<sup>80</sup> and the SSRIs.<sup>81</sup> While favorable case studies, case series, open trials, and a few placebo-controlled investigations have been reported, evidence from well-designed trials has not been confirmed. Therapeutic trials of these agents may be appropriate for some dementia patients with behavioral symptoms who cannot tolerate or do not respond to antipsychotic drugs.

## **WHAT MANAGEMENT STRATEGIES ARE AVAILABLE TO THE PRIMARY CARE PRACTITIONER?**

Successful patient management aims to minimize behavioral disturbances, maximize functioning and independence, and foster a safe and secure environment. To this end, several principles are recommended:

*Schedule regular patient surveillance and health maintenance visits every 3 to 6 months.* Address and treat comorbid conditions, evaluate ongoing medications periodically, and consider initiating drug-free periods. Check for sleep disturbances and provide guidance on proper sleep hygiene. Medicate only as a last resort.

*Work closely with family and caregivers.* Establish and maintain an alliance with caregivers, who can be important sources of information about cognitive and behavioral changes, and often are responsible for implementing and monitoring treatment. Help them establish medical and legal advance directives for patients and update the patient's will early in treatment?<sup>82,83</sup> Suggest that a trusted family member cosign any important financial transaction and take care of paying bills. Discuss long-term care placement in anticipation of future needs, so family members have time to complete the arrangements and begin to make the necessary emotional adjustment. Ultimately, nearly three fourths of dementia patients require admission to a residential long-term care facility and remain for a prolonged time.

*Monitor the health and stamina of caregivers and communicate with their physicians, or treat as needed.* Caregivers' concerns about their own memory lapses should be addressed with counseling or neuropsychological assessment. Support group participation will diminish caregiver distress and can help relieve feelings of anger, frustration, and guilt. Support groups also help confirm that such feelings are common. Community resources, including respite care, are other important sources of help. Studies show that information and emotional support enhance quality of life for patients and family and can delay nursing home placement?

*Establish programs to improve patient behavior and mood.* Set up an exercise routine to continue safe ambulation for as long as possible. Help patients maintain social and intellectual activities as tolerated, especially important family events? Monitor safety and intervene when necessary.

*Encourage caregivers to modulate the environment.* Dementia patients are sensitive to their environment and often do best with moderate stimulation. Too much stimulation may worsen confusion or cause agitation; too little may lead to withdrawal. Encourage families to employ familiar surroundings to enhance mood and maximize existing cognitive functions; to promote a sense of security and predictability through daily routines; and to stimulate memory and orientation through conspicuous displays of clocks, calendars, and to-do lists. Many patients benefit from links to the outside world through newspapers, radios, and televisions. Use of simple sentence structure and frequent reminders about the content of the conversation will enhance communication with the patient.

*Warn families of the hazards of wandering and driving.* Suggest supervised walks to promote regular exercise and encourage the use of door locks or electronic guards to prevent wandering. Encourage registration with Safe Return through the Alzheimer's Association. Patient name tags and medical-alert bracelets also can help locate lost patients. The cognitive impairments of AD diminish driving skills, and a substantial number of even mildly demented patients should not drive because of their visuospatial and planning disabilities,<sup>86</sup> Begin discussions about driving early in treatment and examine driving patterns and transportation needs. Some states, such as California, require physicians to report patients with AD to better monitor their driving skills. A diagnosis of dementia should raise awareness of driving and transportation needs, and patients with advanced dementia should not be driving. There is less consensus on what to tell those with mild dementia. Some

experts believe no person with a diagnosis of AD should drive, while others advise patients to restrict their driving or consider the use of a driving partner, if their history suggests they still are safe drivers. Patients who have a history of traffic mishaps or more significant spatial and executive dysfunction should undergo careful scrutiny.

### **WHAT ARE THE AVAILABLE MEDICAL SPECIALTY AND COMMUNITY RESOURCES?**

Primary care physicians can treat and manage successfully many cases of AD. However, referral to a specialist or specialty AD center is sometimes necessary. Geriatricians, geriatric psychiatrists, psychologists, or neurologists should be consulted when the presentation or history is atypical or complex, especially when the onset is before the age of 60 years. Geriatric psychiatrists and psychologists can provide behavioral management, especially for agitation, psychosis, or violent behavior; management of suicidal behavior or treatment of major depression; individual or family therapy for patients and caregivers; and functional evaluation to make a determination about institutionalization or hospitalization. Neurological consultation is particularly important for patients with parkinsonism, focal neurological signs, unusually rapid progression, or abnormal neuroimaging findings. Neuropsychologists can help clarify uncertainties in diagnosis and the degree and type of impairment, and clinical psychologists can provide psychotherapy, particularly for caregivers. Social workers can offer counseling and link patients and family members with community resources. Activity and physical therapists provide guidance on appropriate levels of physical and group activity, and occupational therapists can evaluate the ability to perform activities of daily living and offer strategies to maximize functioning. Attorneys can assist with wills, conservatorships, estate planning, and other legal matters. For end-of-life issues, some families might also benefit from consultation with a member of the clergy or a medical ethicist.

Community support includes all locally available sources of assistance aimed at maximizing patients' independent living and functioning. The relief can be informal, such as neighbors and friends, and formal, such as home care or family service agencies, the aging or mental health networks, or adult day care centers. Physicians tend to be unfamiliar with these approaches and may want to rely on the Alzheimer's Association or an aging or social service agency familiar with the options. Availability of community resources can be discussed during office visits.

Several specialized services are available, including adult day care and respite care; skilled nursing care provided by the home health agencies; help lines of the Alzheimer's Association; and outreach services, as offered by area agencies on aging and councils on aging, agencies mandated and funded under the federal Older Americans Act. Aging services also can recommend handypersons and homemakers, friendly visitor or companion programs, and housing and legal assistance. Meals-on-wheels arranges food services for the homebound, while senior citizens centers, church and community groups, and hospitals offer transportation options. Organizations providing information and referral for dementia patients and families include the Alzheimer's Association ([800] 2723900), the Geriatric Psychiatry Alliance ([888] 463-6472), the American Geriatrics Society ([212] 308-1414), and the Alzheimer's Disease Education and Referral Center ([800] 438-4380). All offer consumer education, research, and support programs and activities.

### **WHAT ARE THE IMPORTANT POLICY ISSUES AND HOW CAN POLICYMAKERS IMPROVE ACCESS TO CARE FOR DEMENTIA PATIENTS?**

Despite recent progress in the development of new treatments for AD, many patients and caregivers receive inadequate care. One reason is that the precise role of mental health services in the treatment of AD has not been specified. Is AD a medical or psychiatric disease? Is it both? In our

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"nonsystem" of health care for older Americans, a hodgepodge of multiple providers, manifold services, and different (and sometimes competing) financing mechanisms, AD patients tend to occupy a controversial middle ground between psychiatric and medical disorders. In some cases, this "neither-nor" position has led to superior access and reimbursement for some medical treatments, especially compared with patients with chronic diseases or mental disorders. In other cases, patients have been denied eligibility for some state-funded services, such as Medicaid, and have received heightened federal scrutiny of other psychosocial and community services. With reform of the health care delivery system remaining a national concern, clarification of this imprecise middle ground should be a priority. Policymakers need to find ways to deliver quality care to patients, integrating medicine's best understanding of the pathophysiology and natural history of AD with the need for comprehensive and integrated multidisciplinary care.

To maximize the access to care of dementia patients, evidence-based treatment protocols should shape decisions by health care delivery systems. Seamless referral and access to critical services for both patients and caregivers are essential, and reimbursement mechanisms should cover a wide range of sites and services. Payers also should offer physician and staff training and provide sophisticated quality assurance and information processing systems. Finally, special care should be taken to protect the rights of cognitively impaired adults, including the use of advance directives and durable powers of attorney.

Health care delivery in the United States is in the midst of a period of change that may rival in importance even the introduction of Medicare and Medicaid in the mid 1960s. As managed and capitated care come to dominate the health services landscape, federal and state planners will be challenged to develop guidelines to ensure access to primary care providers and specialists; access to core services by underserved inner-city and rural populations; and access to community resources, including self-help groups. It is disturbing that, in the United States, the delivery of care and payment varies so widely by geographic region and socioeconomic status. To overcome these gaps and inequities, planners will need to rely heavily on empirical data, especially in the area of treatment and management of dementia.

Equally necessary is a major change in perception. Policymakers, the medical profession, and payers must recognize that AD and other dementias are chronic diseases like arthritis or coronary artery disease. While the underlying disease is not yet curable, many behavioral and emotional and some cognitive and functional symptoms can be treated, sometimes dramatically enhancing the quality of life of patients and families. Broad access to multidisciplinary care will require a significant commitment of scarce health resources at a time when other pressing medical problems are demanding equal attention. But when we consider the alternatives, the social and economic costs already incurred and the explosive growth in the number of AD patients, we conclude that this is a commitment the nation must make.

### **WHAT ARE THE MOST PROMISING QUESTIONS FOR FUTURE RESEARCH?**

The aforementioned considerations suggest the following research questions: What barriers contribute to the delivery of inadequate or untimely medical services in primary care settings? Areas of investigation might include the following:

- physician knowledge about diagnosis and treatment, and the skills required to assess patients;
- attitudes and beliefs about dementia held by the public and medical professionals;
- fiscal barriers, including access, insurance coverage, and reimbursement and managed care issues;
- demographic and socioeconomic factors, including race, ethnicity, and culture;
- disease complexity and the dependence on specialists to diagnose and treat.

What is the relationship between aging and the increasing prevalence of AD, and how do genetic, environmental, social, and ethnic factors interact in the etiology of disease?

How early and accurately can AD be diagnosed, and what are the most effective measures to use, including cognitive tests, behavioral assessments, neuroimaging and genetic tests? Longitudinal follow-up to determine whether early diagnosis affects outcome should be incorporated in the study design.

Which current and investigational therapies most effectively delay, halt, or mitigate cognitive and behavioral deterioration? what are the relative costs and benefits of current and newer interventions? Areas of investigation might include the following:

- the merits of long-term use of cognition-enhancing pharmacologic therapies;
- the benefits of psychosocial therapies to maximize functioning and quality of life;
- the cost-effectiveness of chronic care programs, including home care, adult foster care, assisted living, nursing home, special care units, and other long-term care;
  - interventions that reduce the risk of caregiver depression and improve tolerance and the capacity to care for patients in the home, including educational materials, counseling, support groups, day care, and respite care.

How do different health delivery systems influence the course of illness, care settings, and impact on the family? How do different disease management models--for instance, primary care vs specialist vs collaborative; psychiatric vs medical; managed care vs fee-for-service--affect diagnosis, treatment, and outcome? which quality indicators are most useful?

What are the best ways to maintain the safety and independence of AD patients? when should patients stop driving, living alone, or participating in other potentially hazardous activities?

What level of care is appropriate and humane for patients with severe end-stage AD? In light of any advance directives that terminal patients may have prepared, is symptomatic treatment warranted? Should life be extended and, if so, for how long?

Whenever possible, health services and outcomes research should be conducted in diverse community populations. Most studies of dementia to date have been conducted in academic or other unrepresentative settings. Differences in the quality and level of care in diverse geographic regions and populations and subgroups should be studied. Minorities in particular face very different treatment and management issues. The use of "natural populations" in controlled community settings offers more practical answers to these questions.

## CONCLUSIONS AND RECOMMENDATIONS

1. Dementia and AD, its most common form, incur substantial costs to society. The diagnosis of AD, moreover, continues to be missed in clinical practice. Alzheimer disease is underreported and unrecognized because many patients do not seek evaluation and family members tend to compensate for deficits. In addition, physicians may fail to recognize the early signs of disease or to diagnose the disorder correctly, even though effective treatment and management techniques are available to enhance quality of life. The lack of a specific diagnostic test for AD means that physicians must conduct a focused clinical assessment and informant interview on patients with suspected AD.

2. The diagnosis of AD is primarily one of inclusion, and the diagnosis usually can be made using standardized clinical criteria. As many patients do not visit a physician for the treatment of suspected dementia at the time of diagnosis, but rather for another medical problem, physicians should be alert to concerns about cognitive decline and evaluate promptly. Progressive memory and other cognitive impairment in a clear state of consciousness is most commonly indicative of AD. Vascular dementia may be overdiagnosed, but its progression is potentially preventable if risk factors for stroke are

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recognized and treatment is initiated.

3. While AD is a complex disorder that ultimately may require treatment by a neurologist, geriatrician, or geriatric psychiatrist, much of its treatment can be managed successfully in the primary care setting. Longitudinal monitoring of therapies and regular health maintenance checkups are essential. New cognitive and functional enhancers may improve memory and other aspects of cognition and function. Emotional and behavior disturbances can be treated, and their resolution can provide significant improvement in quality of life. All psychopharmacologic therapies should be used judiciously in the elderly.

4. Family intervention is critical. Education, counseling, and support can help caregivers cope with feelings of anger, frustration, and guilt in response to a patient's sometimes provocative behavior. Family members benefit from reassurance that their responses are common. Relatives' anxiety about their own memory lapses may respond to counseling, coupled with a neuropsychological evaluation. In some cases, such assessments uncover early symptoms of disease, allowing for prompt treatment and management.

5. Newly evolving delivery systems and reimbursement practices are exacerbating the nation's inadequate and fragmented system of care. Better definition of quality care, based on rigorous quantitative data, will enable policymakers and delivery systems to create new approaches to ensure access to essential medical, psychosocial, and community resources. Given the morbidity and mortality associated with AD, increasing expenditures are essential to fill an already critical medical and social need.

6. Answers to a variety of research questions will help resolve these issues. Investigators need to focus on barriers to care and conduct longitudinal studies, using both naturalistic and treatment-based designs. Cost-effectiveness needs to be assessed for both diagnostic and treatment approaches.

The consensus panel comprised the following members: Gary W. Small, MD, University of California at Los Angeles, and Peter V. Rabins, MD, The Johns Hopkins University, Baltimore, Md, co-chairs; Patricia P. Barry, MD, Boston University, Boston, Mass; Neil S. Buckholts, PhD, National Institute on Aging, Bethesda, Md; Steven T. DeKosky, MD, University of Pittsburgh, Pittsburgh, Pa; Steven H. Ferris, PhD, New York University, New York, NY; Sanford I. Finitel, MD, Northwestern University, Chicago; Lisa P. Gwyther, MSW, Duke University, Durham, NC; Zaven S. Khachaturian, PhD, Ronald and Nancy Reagan Research Institute, Bethesda, Md; Barry D. Lebowitz, PhD, National Institute of Mental Health, Bethesda, Md; Thomas D. McRae, MD, New York University; John C. Morris, MD, Washington University, St Louis, Mo; Frances Oakley, OTR, National Institutes of Health, Bethesda, Md; Lon S. Schneider, MD, University of Southern California, Los Angeles; Joel E. Streim, MD, University of Pennsylvania, Philadelphia; Trey Sunderland, MD, National Institute of Mental Health; Linda A. Teri, PhD, University of Washington, Seattle; and Larry E. Tune, MD, Wesley Woods Geriatric Hospital, Atlanta, Ga. Presenting experts included Stephen J. Barrels, MD, Cornelia K. Beck, PhD, RN, Kathleen C. Buckwalter, PhD, RN, Gene D. Cohen, MD, PhD, D. P. Devanand, MD, David V. Espino, MD, L. Jaime Fitten, MD, Richard H. Fortinsky, PhD, George T. Grossberg, MD, Hugh C. Hendrie, MD, ChB, Dilip V. Jeste, MD, Erie B. Larson, MD, Stephen McConnell, PhD, Thomas E. Oxman, MD, Godfrey D. Pearlson, MD, Murray A. Raskind, MD, and Pierre N. Tarlot, MD. The panel also would like to acknowledge the assistance of Deborah Blacker, MD, ScD, Jeffrey L. Cummings, MD, Alan P. Siegel, MD, Elliott Stein, MD, and Steven Marks.

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# Diagnosis of dementia at the primary care level

Olafsdottir M. Marcusson J.

**In Sweden, as in many other industrial countries, the majority of patients with symptoms of dementia are initially evaluated by a general practitioner (GP). and many do not receive a follow-up assessment by a specialist. Accordingly, GPs play a vital role in identifying patients with possible dementia and undertaking additional diagnostic procedures. Currently, however, the ability of most GPs to perform assessments for dementia is limited. It is important that tests to confirm the presence of dementia be performed uniformly, irrespective of the specialty of the examining physician. Once a diagnosis of dementia has been established and appropriate living arrangements for the patient have been made, the GP should continue to monitor the patient's health status. In Sweden, "dementia teams" or health care professionals have been successful in providing a consistently high level of care to patients with dementia, reducing the incidence of hospitalization for acute illness.**

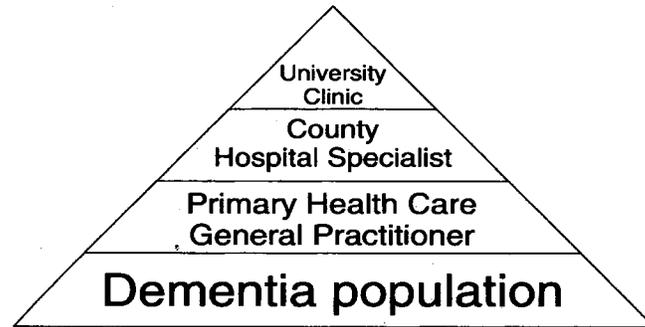
Epidemiologic studies indicate that 5% to 15% of persons over the age of 70 exhibit signs of dementia. Thus, the general practitioner (GP) often encounters persons with possible dementia and has an important role to play in the diagnosis and further management of these patients (Fig. 1). The GP, who often practices in a family-care setting, has a unique opportunity to detect early cases of dementia through extended contact with patients and their relatives and caregivers. In many countries, the GP is often the medical director of extended-care facilities for elderly people, where dementia often occurs. Recently, tacrine hydro-chloride (Cognex<sup>®</sup>, Parke-Davis Pharmaceutical Research Division, Warner-Lambert Company Morris Plains, N J), a specific treatment for Alzheimer's disease (AD), has become available in the United States and in other countries. The availability of symptomatic treatment underscores the importance of early detection of patients with probable AD at the primary care level.

At present, the ability of primary care practitioners to diagnose and treat dementing diseases is limited. Studies from England, the Netherlands, and Australia have shown that, despite a high prevalence of dementia and depression in the elderly, too few cases of these disorders are diagnosed by the GP (1-3). Furthermore, many GP's are reluctant to undertake the procedures necessary to establish a diagnosis of dementia (2, 4). Studies of patterns in Sweden show that diagnostic procedures for dementia are usually undertaken at the specialist level, by geriatricians, psychiatrists, and neurologists. This paper discusses the role of primary health care practitioners in the identification and management of patients with dementia.

## Diagnosis of dementia

It is difficult to clearly differentiate those parts of an evaluation for dementia that should be undertaken by the from those parts that should be conducted by a specialist. In most cases, the GP is responsible for basic diagnostic procedures to detect dementia-like conditions, such as depressive pseudodementia or delirium, and secondary dementia, which can then be addressed with curative or symptomatic treatment. When a diagnosis of primary dementia cannot be ruled out, the patient is usually referred to a specialist for further evaluation and identification of the dementing disorder. However, some GPs also perform these follow-up examinations for dementia. Irrespective of the level at which the diagnostic evaluations take place, the objectives listed in Table 1 must be met.

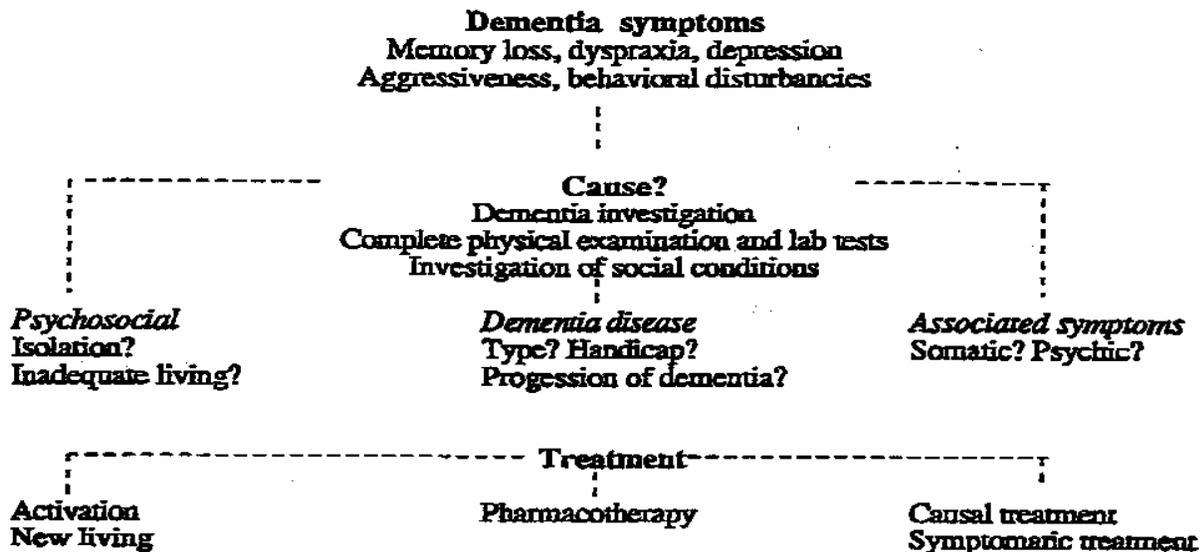
## Alzheimer's Disease



**Fig. 1.** The realities of dementia care. The population of demented persons living in Scandinavia is largely dependent on the primary health care system for diagnostic procedures, treatment, and rehabilitation. In Sweden, many patients with suspected dementing disorders are managed exclusively at the primary care level. Of about 15,000 new cases of dementia per year, less than 5,000 are diagnosed at university clinics. The remaining patients are managed by specialists at county hospitals and by GPs. It is reasonable to assume that diagnostic competencies vary among these three levels of health care. If the diagnostic procedures at one level are not consistent with the overall objectives of dementia investigations (see Table 1), the patient should be referred to a higher level for complementary investigations.

### Patients requiring a complete evaluation for dementia

Everyone who exhibits signs or symptoms of dementia should be medically examined. Although curative treatment may not be available, those who receive supportive care may enjoy a good quality of life for several years, with only limited health care needs, an outcome associated with both personal and economic benefits. All evaluations for dementia must be individualized to the condition of the patient, so that they are both ethical and make appropriate use of human and financial resources



**Fig. 2.** Algorithm illustrating management of the patient with symptoms of possible dementia. Evaluation of the symptoms of dementia demands a comprehensive approach. In addition to dementing diseases, other conditions such as psychosocial disorders or associated somatic conditions may contribute to the clinical picture.

## Managing the patient with possible dementia at the primary care level

At the primary care level, management of patients with dementia should address both medical and social concerns. Necessary actions often require a cooperation between private or community-based custodial care and medical care. Because a problem that can be interpreted as a medical problem, such as extreme hostility, may actually be a response to social factors, such as noisy living conditions, problems that arise must be studied in the broadest possible context (Fig. 2).

**Table 1.** Objectives of clinical evaluation in a patient with possible dementia

- Find treatable causes of symptoms of dementia (AD, brain tumor, depression, delirium, hypothyroidism)
- Verify whether or not dementia actually exists
- Diagnose the dementing disorder (eg, AD, vascular dementia)
- Describe existing clinical damage to the brain
- Describe the functional impairments caused by damage to the brain
- Describe the functional abilities that remain intact
- Perform a complete medical examination and treat associated symptoms and somatic diseases
- Describe the patient's social situation, including the ability to perform- activities of daily living and the quality of family relationships
- Initiate pharmacologic treatment when it is available
- Initiate an appropriate rehabilitation program that focuses on the performance of activities of daily living
- Provide continuous, competent medical care throughout the course of the disease

**Table 2.** Usual components of assessment for dementia

- Medical history (anamnesis)
- Complete evaluation of mental and somatic status, including neurological and psychological examinations
- Blood and urine tests
- Lumbar puncture and examination of cerebrospinal fluid (CSF)
- Brain imaging (CT or SPECT)
- Electroencephalogram (EEG)
- Functional evaluation by occupational therapist
- Psychosocial evaluation
- Final assessment and planning for future care

**Table 3.** Associated somatic conditions in patients admitted by GPs to the Linköping University Hospital with known or suspected dementia

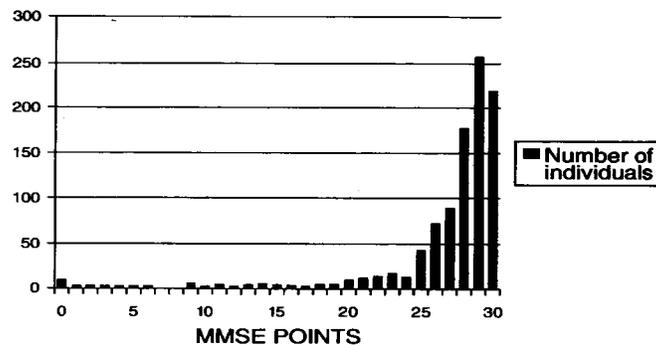
<u>Medical condition</u>	<u>Number of patients</u>
Distal urinary infection	17
Pneumonia	12
Depressive symptoms	8
Cardiac insufficiency	7
Uncontrolled diabetes mellitus	5
Anemia	4
Side effects from drug treatment	4
Gastrointestinal bleeding	3
Constipation	3
Minor stroke/TIA	3

**Conditions diagnosed upon admission to the hospital; some patients had more than one associated somatic condition.**

**Polyclinic visit**

Although hospital admission may be advisable for patients with severe behavioral disorders or those with concurrent somatic disease, most dementia evaluations can be performed polyclinically. The visit, including a complete medical examination, usually requires 1-2 hours. As with all medical investigations, however, the management of each patient must be individualized, with differing amounts of time devoted to physiological, radiological, and clinical chemical investigations. The components of a typical evaluation for dementia are listed in Table 2.

*Medical history* - The medical history, or anamnesis, should include a family history and a summary of any disorders that might have resulted in neurologic or cardiovascular events.



**Fig. 3.** Distribution of Mini-Mental State Examination (MMSE) scores in a population of elderly patients assessed by GPs in Linköping, Sweden. In this study, all people over the age of 70 who visited their GPs (N=963) were assessed using the MMSE examination. Of 102 patients with MMSE scores below 24, 14 had previously been examined and found to be demented. Thus, 86 with low MMSE examination scores were identified as requiring follow-up evaluation.

## Diagnosis at the primary care level

The exact history of the symptoms that seem to be associated with the dementing disorder must be carefully noted, along with their progression and the current extent of the patient's impairment. A complete evaluation of the patient's somatic status is necessary, since undiagnosed disorders often lead to a deterioration in health status that requires hospitalization (Table 3). These somatic conditions were based on an analysis of 49 patients admitted GPs to the Linköping University Hospital because of the presence of dementia, an unbearable home situation, aggressiveness, delirium, anxiety, or a sleep disturbance.

*Determination of neurologic and mental status* - Assessment of the patient's neurologic and mental status is essential, since it provides a basis for a diagnostic evaluation of the dementing disorder. In addition to indicating the extent of cerebral damage that has already occurred, neurologic evaluation is a prerequisite for an appropriate functional assessment.

Memory and cognitive functions can be evaluated in several ways, but the most common method is administration of the Mini-Mental State Examination (MMSE) (5). In one ongoing study undertaken by the University of Linköping, the MMSE was performed on all patients over the age of 70 in the Linköping region who consulted their GPs. Analysis of the first 963 patients and the distribution of MMSE scores are shown in Fig. 3. Although the MMSE is not in itself a sufficient diagnostic instrument to indicate the presence of dementia, it serves as a useful first step in the diagnostic process. The laboratory evaluation that is routinely performed includes tests to detect disorders that may be suggestive of dementia, such as hypercalcemia and hypothyroidism. This evaluation can also include tests aimed at detecting associated somatic disorders (infection, anemia, and malignancy) that may worsen a patient's dementia.

*Lumbar puncture* - Although GPs seldom perform lumbar punctures in Scandinavia, this procedure has a low incidence of complications and does not require hospitalization. Thus, it can easily be performed in the primary care office or clinic. Examination of the cerebrospinal fluid (CSF) provides information about possible damage to the blood-brain barrier and inflammatory or infectious processes. Because levels of tau protein are elevated by 80% to 90% in patients with AD (6), determination of the levels of tau protein in CSF is a new diagnostic marker that is now routinely used at one hospital in Sweden.

*Imaging and functional analysis of the brain* - Computed tomography (CT) of the brain should be performed on most patients who are being evaluated for dementia. Its primary value lies in the fact that approximately 5% of patients evaluated for symptoms of dementia are found to have a treatable condition, such as hydrocephalus, a brain tumor, subdural hematoma, or cyst (7). In other cases, the CT scan may serve as an important adjunct to the other diagnostic procedures used to assess a patient who presents with symptoms of dementia.

Blood-flow measurement, usually with single-photon-emission computerized tomography (SPECT), can be performed at some hospitals, although its value in the assessment of patients with possible dementia remains unclear. Electroencephalography (EEG) can be of value, especially in early cases of dementia, in which the CT scan may be normal and the clinical picture difficult to evaluate. Organic brain disease is usually associated with an abnormal EEG. It is especially important to perform an EEG when signs and symptoms of epilepsy are present.

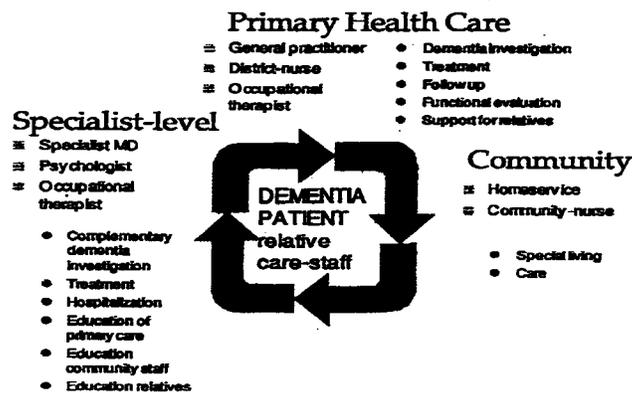
*Functional evaluation* - An evaluation of the patient in the home environment, generally conducted by an occupational therapist, is often a prerequisite for determining which types of care are needed to help the patient achieve an optimal level of function. Such an evaluation is usually necessary

before a patient can be placed in a special home for demented persons.

*Neuropsychological evaluation* - In early cases of dementia, it is often difficult to determine whether or not a pathologic state exists. In such instances, a neuropsychological evaluation can be useful in confirming or disproving the existence of an organic brain disorder.

*Final assessment and planning for future care* - Once all of these tests have been conducted and their results become available, the GP must determine whether or not dementia is actually present. If a diagnosis of dementia is confirmed, the specific type of dementia must be determined, so that any available pharmacologic treatments can be initiated and associated somatic or psychiatric symptoms can be considered.

Family members and other caregivers must receive all necessary information, including, if possible, written reports about the results of the diagnostic procedures that were performed. This information will help them provide the most appropriate care for the patient and may decrease feelings of guilt occasioned by the feeling that they are not doing enough' for their family member. In the long term, provision of adequate information to family members and other caregivers and encouraging them to contact the GP on short notice decreases the need to hospitalize patients with dementia. It is important to clarify which health care professionals are responsible for providing the patient's medical and psychosocial care, respectively, so that caregivers know whom to contact when needed.



**Fig. 4.** Organization of the medical and community care of patients with dementia. Demented persons and their families should receive appropriate medical and supportive care. At the primary care level, "dementia teams" can be formed to address many or the medical and psychosocial problems that arise during the course of the dementing disease. Such teams ensure that the work of the GP is complemented by community services and appropriate living facilities. Patients who are not evaluated or managed by a GP are referred to a specialist.

Although a comprehensive assessment of a patient with possible dementia can ideally be completed in a primary care setting, some GPs limit their evaluations to excluding secondary dementing conditions. In those instances, patients should be referred to a specialist for further diagnostic evaluation and treatment planning.

### Medical care of demented patients in long-term care facilities

In Scandinavia, the GP is often responsible for providing medical care for persons with dementia

## Diagnosis at the primary care level

who live in nursing homes and group homes for demented persons. In Sweden, although most GPs have little time allocated for this work, they are usually involved in treating any acute somatic disorders that arise. There are some local variations in the way in which GPs perform these duties, but a high incidence of admissions to the hospital emergency department is often an indication that the access of demented patients to primary care services is too limited. When an efficient system of primary care is in place, regular time is set aside for monitoring and documenting the condition of demented persons, including their responses to medications. A mechanism that ensures cooperation between a well-educated and competent staff at the patient's living facility and the responsible GP is necessary.

### Ensuring the availability of adequate primary care services

The daily care and medical care of persons with dementia requires both time and *commitment*. Acute problems that require prompt access to competent medical personnel may arise while GPs are examining other patients in their offices or clinics. To avoid errors in patient management, perhaps resulting from a brief telephone conversation, the primary health care system must be able to respond effectively to acute problems involving demented patients. For this reason, "dementia teams" have been established in many communities.

Dementia teams usually consist of one or several nurses and an occupational therapist who visit acutely ill demented patients in their homes or extended care facility. On an as-needed basis, these health care professionals can request the assistance of a GP who is on call for the entire community. Fig. 4 provides a model for the medical care of demented persons within a community. In many cases, a written agreement has been prepared that clearly defines the respective responsibilities of the community, the primary health care system, and the hospital. Such care programs have improved the quality of the community and medical care received by persons with dementia. In the future, when fewer financial resources are likely to be available and the number of demented persons will increase, the efficient organization of these resources will be more important than ever.

### Acknowledgements

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## Alzheimer's Disease

# Classification of dementia and Alzheimer's disease

Morris JC.

**Classification of dementia involves the recognition of its presence, followed by the differential diagnosis of its cause. Informant-based methods for dementia detection can be highly sensitive, even when cognitive impairment is mild. Alzheimer's disease (AD) is by far the leading cause of dementia; standardized clinical criteria result in high diagnostic accuracy rates. Classification of other dementing disorders is less satisfactory, particularly because there is frequent clinical and pathological overlap with AD. After AD, the most common causes of dementia are vascular dementia and dementia in persons with Parkinson's disease. Less common dementias include progressive supranuclear palsy, Huntington's disease, Pick's disease, Creutzfeldt-Jakob disease, and inherited metabolic disorders, most of which are extremely rare. Identifying the cause of dementia is important because some forms can be treated with currently available therapies. In instances involving genetically transmitted disease, genetic testing and counseling of family members may be advisable.**

## **J. C. Morris**

Department of Neurology, The Jewish Hospital, St. Louis, MO, USA  
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The importance of accurate dementia detection and classification is underscored by its impact on public health. The annual cost in the United States of Alzheimer's disease (AD) alone is estimated to be \$58 billion (1). Because dementia prevalence increases exponentially with age (2), demographic changes that result in increased longevity in developed societies ensure that dementia will continue to be an enormous problem. Although differences in definitions of dementia, case-finding procedures, and other methodologies result in varying estimates of the precise frequency of dementia, prevalence rates generally are in the range of 5% to 10% for all persons over age 65. These rates appear to double roughly every 5 years to reach prevalence rates of 25% to 50% for persons over 85 years of age (2). Another impetus for the accurate recognition and differential diagnosis of dementia is the emergence of antidementia drug therapies. In the United States, tacrine (Cognex<sup>®</sup>, Parke-Davis Pharmaceutical Research Division, Warner-Lambert Company, Morris Plains, N J) has been approved since 1993 by the Food and Drug Administration for the treatment of

AD (3). Many other compounds are under investigation for use in AD and other dementing disorders. Dementia is a symptom of brain dysfunction. Because dementia can be produced by many diseases, the dementia syndrome can be associated with a wide constellation of symptoms, mode of onset, course, and responsiveness to therapeutic interventions. This diversity of features can complicate dementia classification, which is already more difficult due to the absence of standardized, widely accepted clinical diagnostic criteria for many dementing disorders. However, uniform diagnostic criteria have been developed and are commonly implemented for the identification of dementia in general (4), and for AD in particular (5). These criteria provide the basis for examining the classification of dementia and AD.

## **Definition and detection of dementia**

Dementia can be defined as the acquired and sustained deterioration of intellectual functions in an alert patient. It thus is distinguished from conditions such as mental retardation and

delirium. Operationally, because of diminished cognitive ability, a demented person conducts everyday activities less well in relation to past performance. Formal criteria for dementia include "the development of multiple cognitive deficits that include memory impairment and at least one of the following cognitive disturbances: aphasia, apraxia, agnosia, or a disturbance in executive functioning [defined as the ability to think abstractly and to plan, initiate, sequence, monitor and stop complex behavior. These disturbances must be sufficiently severe] to cause significant impairment in social or occupational functioning and represent a decline from a previous level of functioning"(4). Criteria also have been proposed that do not require the presence of memory loss to accommodate disorders, such as vascular dementia (6), in which memory may be spared.

### **Differentiating mild dementia from normal age-related changes**

The determination of the presence of mild dementia usually requires a comparison with cognitive changes resulting from normal aging. The distinction between early or very mild dementia and cognitively healthy aging can be very difficult and is impracticable for large-scale population surveys, in which case-finding typically is restricted to moderate-to-severe dementia as identified by cut-off scores on brief cognitive tests (7, 8). However, the number of dementia cases undetected by this approach is large; the prevalence of mild dementia may be three times greater than for severe dementia (2). Moreover, the advent of promising therapeutic agents for dementia places a premium on detecting dementia in its earliest stages.

Although cerebral processing resources required for attention-demanding tasks and episodic memory are adversely affected with age, age-related cognitive changes generally occur so gradually that they are considered nonprogressive. In addition, they do not interfere substantively with everyday life, particularly

because use of environmental cues or other compensatory strategies (e.g., list making) can minimize deficits (9, 10). A knowledgeable observer of the patient's performance in usual activities generally is best able to determine whether everyday cognitive function is impaired. In contrast, self-reported memory complaints from the patient correlate better with the presence of depression than with dementia (11, 12).

Informants (usually the patient's spouse or adult child) also can reliably detect the very earliest manifestations of dementia (13). Indeed, informant-based methods may be more sensitive than neuropsychological tests for very mild dementia, at least in some circumstances (14), in part because the confounding effects of age, education, and other demographic variables on cognitive test performance (15, 16) are avoided. Also, informants are best able to judge the essential criteria of how cognitive abilities have changed in relation to past performance and whether the changes are sufficient to impair everyday function. The sensitivity of informant-based methods for very mild AD is illustrated in Fig1.

### **The use of mental status testing**

Mental status testing is useful to document impaired cognition and to monitor cognitive decline. Full-scale neuropsychological batteries systematically evaluate the major cognitive functions affected by dementia: memory (primary and secondary; verbal and non-verbal), problem solving and sequencing (executive functioning), language, visuospatial abilities, attention, and psychomotor skills, including timed tasks. Because such batteries can take several hours to administer, brief cognitive tests often are used to rapidly assess a limited number of cognitive abilities for screening purposes. The Information-Memory-Concentration test, in both its original (18) and shortened (19) forms, and the Mini-Mental State Examination (20) are examples of commonly used brief cognitive tests. As noted above, however, cognitive measures

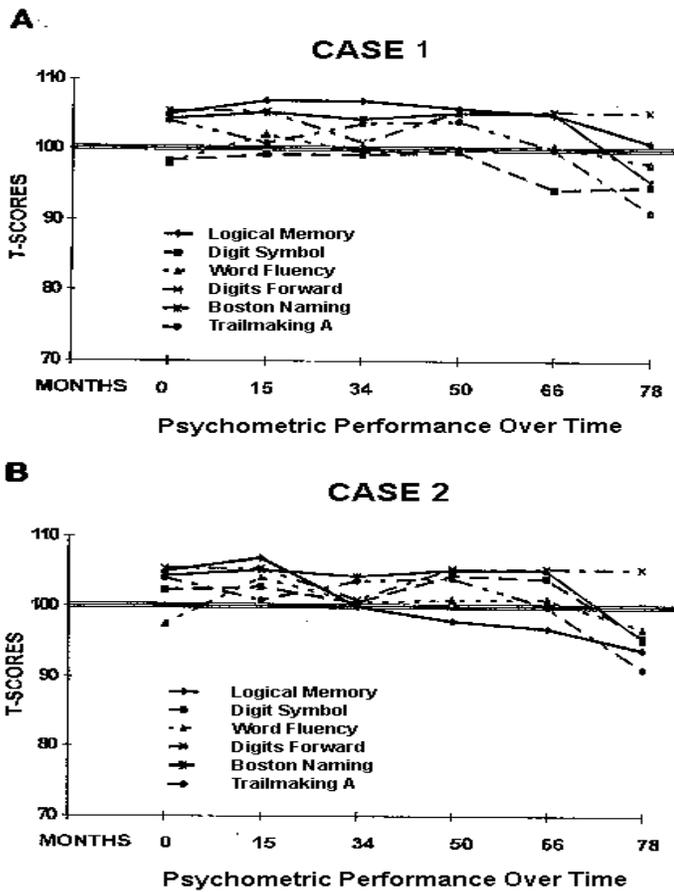
may be affected by demographic factors and may be insensitive to very mild dementia. In addition, they rarely measure deficits over the entire course of dementia because of floor and ceiling effects.

Global clinical assessment scales typically incorporate data from informant interviews and the patient's performance into an overall severity rating that is a clinically meaningful measure of the patient's disability. They also are less subject to floor and ceiling effects and thus measure

progression throughout the course of dementia. Of the several global scales available, the Global Deterioration Scale (21), the CAMDEX (22), and the Clinical Dementia Rating (23) are among those most widely used.

**Classification of dementing disorders**

Many disorders are known to cause dementia (Table 1). In the absence of a biological marker for AD or many of the other common dementing illnesses, differential diagnosis remains in the hands of the clinician. Autopsy confirmation of the clinical diagnosis should be sought whenever possible, particularly because clinical diagnostic accuracy for some dementias is poor. For example, clinicopathologic studies indicate that the clinical diagnosis of vascular dementia is inaccurate in the majority of cases (24, 25). Valid and standardized clinical diagnostic criteria are needed for vascular dementia and other non-Alzheimer dementias.



**Fig. 1.** Changes associated with normal aging and mild AD. Panels A and B. - Psychometric performance is shown from initial (time 0) through last assessment (6.5 years later) on two control participants in a longitudinal study of aging. Case 1 (A) remained cognitively normal by clinical evaluation until death (4 months after last assessment). Case 2 (B) was judged cognitively normal until the last assessment. 8 months before a sudden death at age 78. At this final assessment, the patient's daughter reported minor but consistent changes in cognitive ability and the patient was diagnosed on clinical grounds as being very mildly demented. T-scores for the measures (WMS Logical Memory, Digit Symbol, Word Fluency, Digits Forward, Boston Naming, Trailmaking A) are based on the distribution of test performances of 83 control subjects (mean age=71.6 +/-4.9 years) and have a mean=100 and SD=5. Although minor decline on some measures was observed for both Case I and Case 2 at last assessment, their psychometric performances remained "normal" There was no brain pathology in Case 1, whereas the neuropathology for Case 2 showed well-established AD. Panel C. - Survey photomicrograph (x 100, Bielschowsky silver method) of frontal neocortex at gray-white-matter junction (bottom) from Case 2. There is a high density of diffuse and neuritic plaques in the frontal neocortex, indicating that histological AD already was firmly established at the time dementia was reaching the threshold of clinical detection. (Photomicrograph courtesy of Daniel W. McKeel, Jr, ME.) Reprinted from Morris 1994 with permission (17).



**Alzheimer's disease**

AD, with or without comorbid conditions, is by far the leading cause of dementia, accounting for 75% or more of all pathological diagnoses of dementing disorders (26). The overall clinical picture is characteristic; diagnostic accuracy for AD is in the range of 85% to 95% (27, 28). Memory impairment is the salient cognitive feature of AD and usually is the presenting symptom, although personality changes may occasionally herald the disorder. Gradual onset

and progression of symptoms is typical.

In mild stages, forgetfulness (characterized by repetition of questions and misplacement of items without independent retrieval), minor temporal and geographic disorientation, difficulties with calculation (including errors in managing household finances), and reduced insight and initiative are typical. Social skills and basic self-care abilities generally are preserved in this stage and the patient appears normal to the casual observer.

**Table 1.** Disorders known to cause dementia\*

<u>Category</u>	<u>Examples</u>
Cerebral neuronal degeneration	<ul style="list-style-type: none"> <li>• Alzheimer's disease</li> <li>• Pick's disease</li> <li>• Parkinson's disease</li> <li>• Huntington's disease</li> <li>• Progressive supranuclear palsy</li> </ul>
Acquired cerebral disorders (some potentially reversible)	<ul style="list-style-type: none"> <li>• Vascular dementia: multi-infarct dementia, Binswanger's disease</li> <li>• Multiple sclerosis</li> <li>• Intracranial neoplasms</li> <li>• Trauma (including subdural hematoma)</li> <li>• Hydrocephalus</li> <li>• Transmissible spongiform encephalopathies (eg, Creutzfeldt-Jakob disease)</li> </ul>
Potentially reversible disorders	<ul style="list-style-type: none"> <li>• Metabolic disorders: hypothyroidism, renal dialysis</li> <li>• Toxic/metabolic disorders: chronic drug intoxication, alcoholism, malnutrition (eg, vitamin B12 deficiency)</li> <li>• Infections: HIV (AIDS), neurosyphilis, tuberculous or bacterial meningitis, cryptococcosis, acute viral encephalitis</li> <li>• Major depression</li> </ul>

\* Adapted from Morris 1994 with permission (17).

In moderate stages, memory for recent events is rapidly lost and only highly learned material is recalled. Language comprehension and output are compromised. Disorientation and inability to handle money, make purchases, or accomplish routine chores (e.g., washing dishes) without supervision is characteristic. Supervision also is needed for self-care functions such as dressing. Troublesome behaviors, including delusions, hyperactivity (restlessness; wandering), verbal and physical aggression, and hallucinations often complicate the moderate stages of AD.

In advanced AD, total dependence is the rule and the patient eventually becomes uncomprehending, mute, and bedridden. Death usually results from concomitant illnesses such as aspiration or urosepsis. On average, the duration from onset of AD to death is 8 to 10 years (29).

The general course of AD as outlined above is subject to individual variability. Indeed, variations in age of onset, presenting symptoms, rate of progression, and presence or absence of family history of dementia comprise a substantial clinical heterogeneity for AD. Genetic heterogeneity for AD already has been established (30). Phenotypic and genotypic variants suggest that, rather than representing a single disorder, AD may have multiple etiologies that share a final common pathway resulting in neuronal death.

### Overlap syndromes

After AD, cerebrovascular disease and Parkinson's disease are the second and third leading causes of dementia (26). They are frequently found in association with AD, leading to the concept of "mixed dementias." At present, there is nosologic confusion regarding these mixed dementias because there are no clear methods to determine the relative contribution of each concomitant disorder to the dementia.

A complicating factor in attempts to classify these overlap conditions has been the failure to consistently distinguish *association* and *causality*; for example, the presence of a cerebral infarct in a brain of a demented person

with AD does not necessarily imply that the stroke had anything to do with the dementia.

This dilemma also extends to the syndrome of diffuse Lewy body disease, which may represent part of the spectrum of dementias associated with Parkinson's disease. It has been difficult to unambiguously correlate the clinical features with the presence of cortical Lewy bodies rather than with the concomitant Parkinson's disease (31) or the frequently associated AD (32). Clinico-pathological correlations of prospectively studied patients fulfilling recently proposed clinical criteria for vascular dementia (6, 33) and diffuse Lewy body disease (34) are needed to determine those features that distinguish these conditions from AD.

Patients with AD are prone to develop other age-associated illnesses. Many comorbidities have the potential to add to cognitive impairment, but may be amenable to specific therapy. Depression and overmedication are among the most frequent disorders complicating AD (35).

### Vascular dementia

Vascular dementia results from brain injury caused by a cerebrovascular disorder (36). Ischemic rather than hemorrhagic disorders are generally regarded as playing the primary role in its development. Roman et al have argued that the essential elements in establishing a diagnosis of vascular dementia are

- 1) confirming that true dementia, as opposed to a focal neurobehavioral deficit, is present,
- 2) ascertaining the presence of cerebrovascular disease by patient history, physical examination, or brain imaging studies, and
- (3) establishing a causal link between the two disorders (33).

The diagnostic value of the Ischaemic Score, originally proposed by Hachinski et al.(37) as a means of distinguishing between vascular and "degenerative" dementias, such as AD, remains controversial (36). Although a number of revisions to this assessment tool have been

proposed, much work remains to clarify the meaning of the 13 descriptive terms (eg, "abrupt onset;" "stepwise deterioration") on which the scoring system is based.

Estimates of the proportion of patients whose dementia is attributable to vascular dementia have varied widely. Although Mirsen & Hachinski estimated that 15% to 19% of persons with dementia have vascular dementia and that an additional 7% to 18% have mixed dementia, consistent with O'Brien's conclusion that there is a "significant vascular component" in one-third of patients with dementia (39), clinico-pathological data indicate that most patients clinically diagnosed with vascular dementia may in part reflect population differences (41), but more often relates to the lack of validated diagnostic criteria and assessment instruments for this condition (42).

Although many remain incompletely understood, several mechanisms for the development of vascular dementia have been proposed (Table 2). Of these factors, those that play a role in its development, the volume, number, and location of cerebral lesions are believed to be the most important (35).

Vascular dementia is often divided into cortical and subcortical (or frontal-subcortical) syndromes (43, 44). Cortical vascular dementia is characterized by repeated atherothrombotic or cardioembolic strokes, obvious sensorimotor deficits, more severe aphasic disturbance when present, and an abrupt onset of cognitive failure (45). Subcortical vascular dementia is associated with pseudobulbar signs, isolated pyramidal defects, depression or emotional lability, and a frontal behavioral syndrome whose symptoms include mild memory impairment, disorientation, poor response to new experiences, limited interests, decreased ability to make associations, inattention, difficulty in passing from one idea to another, and perseveration.

Unlike AD, patients with vascular dementia may exhibit deterioration, improvement, or fluctuating clinical course (46). Lechner et al. studied 94 patients with clinically diagnosed multi-infarct dementia over a 5-year period and

found that 6.4% experienced improvement, 43% died (with an annual mortality rate of about 13%), and 41% of survivors remained independent during the observation period (47).

The traditional treatment for patients with vascular dementia is the prevention of further strokes through antihypertensive therapy, administration of antithrombotics, and carotid endarterectomy (35). Therapies currently under investigation include administration of calcium antagonists such as nimodipine, glutamate antagonists such as N-methyl-D-aspartate, hemorrheologic agents such as pentoxifyline, and dopaminergic antagonists such as bromocriptine.

### Parkinson's disease

One of the most common neurologic disorders, idiopathic Parkinson's disease affects 80 to 200 people per 100,000 in the general population (48). It has been established that the *risk* of dementia among patients with Parkinson's disease greatly exceeds that of other individuals of the same age, but estimates vary concerning the actual percentage of patients with Parkinson's disease who also have dementia. In a population-based study, Sutcliffe et al found that the prevalence of dementia in patients with Parkinson's disease was 11% (49), whereas Mayeux et al, reporting on a community-based study, determined that the overall prevalence of dementia in this population was 41.1 per 100,000, ranging from zero in persons younger than 50 years to 787.1 in those  $>80$  (48).

It has been shown that first-degree relatives of persons with both dementia and Parkinson's disease have at least six times the risk of developing dementia compared with nondemented persons with Parkinson's disease (50). In addition, first-degree relatives of patients with AD have an approximately three times higher risk of developing Parkinson's disease than the general population (51). This familial aggregation suggests that there may be a common genetic etiology for AD and

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Parkinson's disease (35). Although the neuropathologic basis for the dementia found in patients with

**Table 2.** Pathophysiologic mechanisms of vascular dementia

<u>Factor</u>	<u>Pathophysiologic consequences</u>
Volume of injury	Eventually, infarct size reaches a critical threshold and overcomes the brain's compensatory capacities
Number of injuries	Multiple small or large infarcts have: <ul style="list-style-type: none"> <li>• additive effects that are equivalent to a large cumulative volume</li> <li>• multiplicative or synergistic effects</li> </ul>
Location of injury	Infarct damage to the following areas has the most marked impact on higher cerebral function: <ul style="list-style-type: none"> <li>• cortical sites, including association areas and the limbic cortex</li> <li>• subcortical sites, including gray matter nuclei or white matter pathways between association areas or between subcortical and cortical regions of the limbic system</li> </ul>
Distal field insufficiency	<p>Marginal or reduced cerebral blood flow results in:</p> <ul style="list-style-type: none"> <li>• distal field infarction, including "granular cortical atrophy"</li> <li>• distal field ischemia, with "misery perfusion"</li> </ul> <p>White matter ischemia due to small-vessel disease, leads to "chronic ischemia" and "incomplete infarction" of the cerebral white matter; mental especially hypertensive changes result from:</p> <p><i>Penetrators</i></p> <ul style="list-style-type: none"> <li>▪ severity or amount of white matter damage</li> <li>▪ location-specific effects; with frontal white matter involvement resulting in disconnection or diaschisis</li> <li>▪ associated subcortical infarction</li> </ul> <p><i>Arteriopathy of medulla</i></p>
Concurrence of vascular disease and AD	<p>Leads to:</p> <ul style="list-style-type: none"> <li>• additive or multiplicative effects between infarction and underlying AD</li> <li>• chronic ischemia or microinfarcts (due to amyloid angiopathy or other arteriopathy associated with AD) exacerbating mental changes</li> </ul>
Other unknown or incompletely understood mechanisms	<p>May lead to:</p> <ul style="list-style-type: none"> <li>• delayed transneuronal degeneration</li> </ul> <ul style="list-style-type: none"> <li>• brain atrophy or neuronal loss secondary to hypertension or other vascular factors</li> <li>• neurotransmitter deficiencies resulting from damage to specific regions or pathways</li> </ul>

\*Adapted from Tatemichi et al. 1994 with permission (36).

Parkinson's disease is still under investigation, the

primary causative factors are believed to be concurrent AD (52) and primary nigral degeneration (50). The role of cortical Lewy bodies in the development of dementia is unknown, as they are commonly detected in Parkinson's disease regardless of whether cognitive dysfunction was also present (54).

In Parkinson's disease, certain types of cognitive impairment have been reported in patients without overt dementia. These include bradyphrenia (inattention and diminished concentration, reaction time, and recent memory) (55) and impaired perceptual input (56), facial recognition, visual discrimination (57), implicit memory (58), and intentional set shifting (59). The cognitive impairment in demented patients with Parkinson's disease is similar to AD, in that recent and retrograde memory is impaired (60), but demented Parkinson's patients tend to have worse verbal memory than equally impaired patients with AD (61). Implicit and explicit memory (as manifested in motor skill learning) (62) and performance in visuospatial tasks also tends to be worse (60) in Parkinson's.

### **Progressive supranuclear palsy**

Progressive supranuclear palsy affects 1 to 4 people per 100,000 and has a usual age of onset of 60 to 70 years (63). Pathophysiologic changes include neuronal loss, gliosis, and neurofibrillary tangle formation in the substantia nigra, basal forebrain, and other subthalamic areas (35). Levels of dopamine, acetylcholine, and  $\gamma$ -aminobutyric acid (GABA) may be reduced in these regions.

Progressive supranuclear palsy is marked by supranuclear gaze palsy, dysarthria leading to mutism, dystonic rigidity, and gait and postural disturbances (64). Personality changes,

including depression, indifference, and apathy, are common and dementia occurs in 20% to 60% of patients (63). Although memory performance may be better in these patients than in those with AD, verbal fluency and other language tasks are often severely impaired (35). Attention deficits also tend to be prominent (61). Pharmacotherapy may be effective in treating certain aspects of progressive supranuclear palsy (35). Dopaminergics, including levodopa, bromocriptine, and pergolide, may improve its motor function, as can idazoxan, a selective  $\alpha_2$  presynaptic inhibitor (65). In addition to treating the emotional disorders associated with this disease, tricyclic antidepressants can also improve swallowing (35). Physostigmine has shown initial promise in improving long-term memory and visual attention.

### **Huntington's disease**

Huntington's disease is an autosomal dominant disorder with a prevalence of 4 to 8 people per 100,000 (66) and a peak age of onset between 35 and 50 years. Atrophy or flattening of the caudate nucleus and putamen in the ventrolateral wall of the lateral ventricle is the main gross pathological change (35). Other findings include loss of cerebral white matter and nerve cells, astrocytosis, and reduced brain concentrations of GABA and glutamic acid decarboxylase. Usual clinical manifestations include chorea, ocular motor dysfunction, impaired performance of fine motor movements, postural instability, apathy, irritability, poor impulse control, depression, and cognitive impairment that begins during the early stages of the disease.

Although verbal recall and recognition are similarly impaired in patients with Huntington's disease and AD, patients with Huntington's disease may make fewer errors in performing recognition tasks (67). Impaired memory in

patients with Huntington's disease seems to relate to their inability to concentrate and develop information retrieval strategies (61). Hodges et al found that patients with Huntington's disease tended to perform worse than comparably impaired patients with AD in tasks involving word retrieval, phonetic verbal fluency, vocabulary, and copying geometric figures (68). Progressive loss of visual-verbal judgment (69) and general visuospatial function (70) are also common in patients with Huntington's disease.

Patients with Huntington's disease are often treated with dopamine antagonists, such as tetra benazine, to reduce chorea, and with antipsychotic agents and antidepressants (35). Propranolol may be effective in reducing impulsive behavior. No effective treatment for cognitive impairment associated with Huntington's disease has been found.

### **Pick's disease**

Pick's disease is a rare disorder characterized by circumscribed frontal and rostral temporal atrophy (71). Microscopic sections of the neocortex reveal numerous Pick bodies, intracytoplasmic argyrophilic neuronal inclusions about the size of a nucleus that are composed of filaments, microtubules, and occasional short segments of paired helical filaments. Pick's disease usually has its onset between the ages of 50 and 70 years (72).

Whereas memory impairment and temporospatial disorientation are the most frequent early signs of AD, patients in the early stages of Pick's disease usually exhibit mood disturbances, irritability that alternates with incoherent joviality, early loss of social awareness, aberrant behaviors, bulimia, verbal stereotype, and progressive language impairment that eventually leads to mutism (72).

### **Creutzfeldt-Jakob disease**

Creutzfeldt-Jakob disease is a rare prion-associated spongiform encephalopathy (73). Prion diseases are both genetic and infectious

(74). Although both familial and sporadic forms of the disease have been reported, the majority of cases are sporadic.

Gross pathological features include cerebral cortical atrophy with ventricular enlargement, and atrophy of the basal ganglia and cerebellar rolls. Numerous vacuoles of different sizes are present on microscopy throughout the gray matter of the neocortex, corpus striatum, thalamus, molecular layer of the cerebellum, and upper brain stem (75). This spongiform vacuolization is accompanied by neuron loss and gliosis. Kuru plaques, composed of prion proteins, may also be found throughout the brains and in the spinal cords of some patients who live for more than 1 year.

Clinically, Creutzfeldt-Jakob disease is characterized by rigidity, myoclonus, ataxia, blindness, aphasia, periodic EEG changes, and rapidly progressive dementia. Many patients die within 1 year of disease onset (74).

### **Metabolic disorders that cause dementia**

Rare inherited metabolic disorders may also cause dementia. Such disorders include disorders of metal metabolism, peroxisomal disorders, lipoprotein disorders, lipidoses of unknown origin, mitochondrial disorders, lysosomal storage disorders, carbohydrate disorders, and miscellaneous disorders (76). These disorders are summarized in Table 3. The differential diagnosis of patients presumed to have metabolic dementing disorders is crucially important, because the cognitive impairment associated with such disorders as Wilson's disease, adreno-leukodystrophy, adrenomyeloneuropathy, and cerebrotendinous xanthomatosis, can often be reduced or even reversed with appropriate, timely treatment. In some instances, genetic counseling and prenatal diagnosis may be advisable.

### **Conclusion**

Although it is the most common form of dementia, AD-related dementia may be associated with other dementing illnesses including

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vascular dementia and Parkinson's disease. Other, less common causes of dementia, including progres-sive supranuclear palsy, Huntington's disease, Pick's disease, Creutzfeldt-Jakob disease, and a variety of rare metabolic disorders, can usually be distinguished from AD by distinctive physical signs and symptoms that appear before or in tandem with the onset of cognitive impairment.

**Table 3. Summary of metabolic disorders that cause dementia in adults**

<u>Classification</u>	<u>Disorder</u>	<u>Pathophysiology</u>	<u>Clinical characteristic</u>
Disorders of metabolism	• Wilson's disease	• Error in copper metabolism	• Hepatic cirrhosis; memory difficulties and other cognitive impairment in 6% of patients
	• Hallervorden-Spatz disease	• Excess deposition of iron-containing pigments in the brain	• Dementia
	• Fahr's syndrome	• Excess deposition of calcium and iron in the brain	• Dementia
Peroxisomal dis. progression; impaired frontal-executive functions and memory in 50% of patients	• Adrenomyeloneuropathy	• Abnormal accumulation of saturated very long chain fatty acids in the brain, spinal	• Spasticity, weakness, impaired vibratory sense, bladder dysfunction, adrenal insufficiency, relatively slow
	• Adrenoleukodystrophy	• Abnormal accumulation of saturated very long chain fatty acids in the brain	• Seizures, behavioral disturbances, rapid progression; dementia in nearly all patients
Lipoprotein disorders	• Cerebrotendinous xanthomatosis	• Defective bile acid synthesis, with increased cholestanol formation	• Tendon xanthomas, cataracts, dementia, pyramidal weakness and spasticity, cerebellar ataxia, seizures, peripheral neuropathy, osteoporosis, behavioral abnormalities, psychiatric symptoms; dementia that may manifest in childhood or not until the sixth decade
Lipidoses of unknown origin	• Kuf's disease	• Possible error in metabolism of lysosomal and Golgi membranes	• Progressive myoclonic epilepsy, ataxia, movement disorders, behavioral changes; dementia
	• Membranous lipodystrophy	• Unknown	• Bone cysts, pathologic fractures, seizures, mania; dementia, including memory impairment, disorientation, disinhibition, perseveration
Mitochondrial disorders	• Mitochondrial encephalopathy with lactic acidosis and stroke-like episodes (MELAS)	• Defect in NADH coenzyme Q reductase of the respiratory chain	• Strokes, seizures, lactic acidosis, ragged-red fibers exercise intolerance, limb weakness, short stature, headache, hearing loss
	• Myoclonus epilepsy with ragged-red fibers (MERRF)	• Probably a combined partial defect of all respiratory chain complexes requiring mitochondrial DNA-encoded subunits	• Myoclonus, seizures, ataxia, weakness, short stature, hearing loss, lactic acidosis, ragged-red fibers; dementia
Lysosomal storage disorders	• Metachromatic leukodystrophy	• Arylsulfatase A deficiency	• Ataxia, pyramidal tract disease, rigidity, athetosis, dystonia, pseudobulbar palsy, peripheral neuropathy, inertia, disinhibition, disorganization; dementia primarily characterized by memory impairment
Carbohydrate dis-sphincter orders	• Adult polyglucosan body disease	• Polysaccharide deposits in the central nervous system and peripheral nerve axons	• Peripheral neuropathy, pyramidal tract signs, problems; dementia

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| Other metabolic disorders | <ul style="list-style-type: none"> <li>• Lafora's disease</li> <li>• Neuronal intranuclear hyaline inclusion disease</li> <li>• Mast syndrome</li> </ul> | <ul style="list-style-type: none"> <li>• Polyglucosan deposits in the brain</li> <li>• Hyaline deposits</li> <li>• Unknown; autosomal recessive disorder within Amish community of Eastern U.S.</li> </ul> | <ul style="list-style-type: none"> <li>• Myoclonus, epilepsy; dementia</li> <li>• Choreoathetosis, dysarthria, ataxia, abnormal eye movements, decreased sensation; dementia</li> <li>• Gait disorder, dysarthria, cerebellar disease, pyramidal tract disease, athetosis, dementia</li> </ul> |
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# Attitudes of Older Adults on Being Told the Diagnosis of Alzheimer's Disease

*Suzanne Holroyd, MD,<sup>1</sup> Diane G. Snustad, MD,<sup>1</sup> and Zona L. Chalifoux, RN, PhD<sup>1</sup>*

**OBJECTIVE:** Controversy exists as to whether Alzheimer's disease (AD) patients should be told their diagnosis, yet no research has been done examining older patients' attitudes on this topic. This study examines patient's attitudes toward this topic.

**DESIGN:** A prospective, community-based study. Participants read vignettes of two patients, one with AD and one with terminal cancer, and then answered questions regarding their attitudes toward these illnesses.

**SETTING:** A community-based retirement community in Charlottesville, Virginia.

**PARTICIPANTS:** One hundred fifty-six community-dwelling older persons (mean age 79.7 +/- 6.9 years).

**MEASUREMENTS:** A structured questionnaire disclosed demographic data (age, sex, race, religion, marital status), personal experience with cancer and AD, and opinions about being told the diagnosis of these diseases.

**RESULTS:** Most participants (n = 124, 79.5%) responded that they would prefer to know if they had AD, but the number was significantly fewer (Fisher exact test,  $P < .001$ ) than those who would want to know if they had terminal cancer (n = 143, 91.7%). Interestingly, significantly fewer married subjects would want their spouse to know if the spouse had either illness. Only 65.7% (n = 69) of subjects would want their spouse to know if the spouse had AD (Fisher exact test,  $P = .008$ ), whereas for cancer, 80.2% (n = 77) would want their spouse to know if the spouse had cancer (Fisher exact test  $P < .001$ ). No demographic variables distinguished subjects who did from those who did not want to know the diagnosis for themselves or their spouses for either AD or cancer. Among the reasons some subjects

gave for wanting to know of the diagnosis of AD was being able to consider suicide.

**CONCLUSION:** Although these results may support disclosure of diagnosis for most patients with AD, clinical and ethical issues remain in individual cases. *J Am Geriatr Soc 44:400-403, 1996.*

From the <sup>1</sup>Department of Psychiatric Medicine, University of Virginia School of Medicine: Department of Medicine, Division of Geriatrics, University of Virginia School of Medicine; and James Madison University, College of Integrated Science, Charlottesville, Virginia.

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Address correspondence to Suzanne Holroyd, MD, Blue Ridge Hospital, Drawer D, Charlottesville, VA 22901.

The physician practice of either withholding or informing patients of a diagnoses of serious illness has changed dramatically from one of withholding "bad news" to one of full disclosure. This has been true especially since the 1970s.<sup>1</sup> A questionnaire administered to physicians in 1961 found 90% indicated they would not tell a cancer patient his diagnosis, whereas the same questionnaire in 1977 revealed a complete reversal, with 97% indicating a preference for telling a cancer patient the diagnosis.<sup>2</sup> Reasons for this change may include improved treatments for cancer and issues of legal liability,<sup>1</sup> but societal changes supporting the "patient's right to know" have arguably been the most important reason.<sup>1</sup> In addition, studies of cancer patients' attitudes also support this viewpoint, revealing a patient's desire to be kept well informed?<sup>3,4</sup> It has also been noted, however that older people are more likely to prefer the "older nonparticipatory patient role, compared

with younger patients.<sup>3</sup>

Although "truth-telling" is now well established for cancer, some controversy remains in regard to dementing illnesses such as Alzheimer's disease (AD). A recent article reviewed both sides of this issue<sup>5</sup> and noted the dilemmas clinicians may confront. For example, the diagnosis of Alzheimer's disease is still, for the most part, made on clinical criteria and is thus uncertain, especially in the early stages of the disease. Further, AD patients are often brought in by others (family) rather than by complaints of the patients themselves, who often don't think anything is wrong and don't want an evaluation or diagnosis?<sup>6</sup> In addition, issues of competency and decision-making capacity arise with such patients. Although a diagnosis of dementia does not necessarily mean a patient is incompetent to make decisions,<sup>7</sup> it may be difficult to find a time, after the diagnosis is reliably made, when the patient can still fully comprehend the information.

Although much has been written about how to make the diagnosis of AD, most authors, including those of standard textbooks,<sup>8-10</sup> do not address the issue of whether to inform patients of their diagnosis. Two articles that do mention this as an issue advocate discussion of the diagnosis with the patient.<sup>6,11</sup>

In contrast to the research with cancer patients, little research has been done on this issue in Alzheimer's disease. To our knowledge, the only study of patient attitudes done in a group of 224 general medical outpatients, of whom only 18.5% were older than age 65, the age where one would most likely be faced with this illness, and the majority of subjects were less than age 50. Patients read a vignette of a patient with AD, then answered questions about whether they would want to be told the diagnosis and why. The study revealed that more than 90% of the patients would want to be told the diagnosis,<sup>12</sup> The study also found that those wanting to know were more likely to know someone who had dementia.

As noted above, older patients are more likely to prefer "the older nonparticipatory patient role" in regard to truth-telling for cancer. In this study, we examined the attitudes of community-dwelling older people toward being told of the diagnosis of

Alzheimer's disease. To further examine whether the subjects were responding to *any* bad" diagnosis or whether there were specific differences regarding an Alzheimer's disease diagnosis, the older people sampled were also asked their attitudes toward being told of a diagnosis of terminal cancer.

## METHODS

A sample of community-dwelling older people was obtained from a private retirement community in Charlottesville, Virginia. All subjects aged 65 and older (n = 237) were included in the study. A structured questionnaire (available from the authors) was sent to each subject. The questionnaire included a cover letter explaining the purpose of the study and asked for demographic information including age, sex, race, religion, and marital status. Two vignettes were then presented, one of a patient with AD and another of a patient with terminal cancer. The vignettes from the questionnaire are given below.

### Vignette 1

At age 66, Mrs. Doe has an illness that is changing her. She has trouble remembering and becomes confused about the date. She is no longer able to do her bills and forgets people's names. She notices these changes and is upset by them. Her family notices too and takes her to the doctor. The doctor does a variety of tests and determines the disease causing these changes. The disease has no treatment, and her memory and ability to think will get worse over time. Over time, Mrs. Doe will be unable to drive. The doctor explains that with this disease, no one can predict which symptoms Mrs. Doe will have in the future, but they can discuss possible symptoms that she may experience. She may become unable to dress herself and do other simple tasks. She may wander off and not be able to find her way back home. She may become unable to use the toilet and require a diaper. She may undergo personality changes and become irritable, moody, and difficult for the family to handle. She may not recognize

people in her family. She may stop being able to talk. She may start hearing and seeing things that are not there.

The above description is one of a patient who could have Alzheimer's disease.

### Vignette 2

Mr. Doe has noticed his clothes becoming much looser over the last several months. He has lost his appetite and has much less energy than he used to have. He has noticed a dull pain somewhere in his hip bone. His doctor examines him, does a variety of tests, and determines the disease causing these changes. The disease has no cure and will get worse with time, eventually resulting in death. Although the doctor cannot precisely predict which symptoms Mr. Doe will experience in the future, he tells Mr. Doe what possible symptoms he may have. Over time, Mr. Doe may continue to lose weight and be unable to eat. He may develop severe pain. He could become extremely nauseated. He may lose the ability to do activities or work he enjoys. He may become unable to care for himself.

The above description is one of a patient who could have terminal (incurable) cancer.

Following each vignette were questions regarding the subject's personal knowledge of others with the illness, questions regarding the subject's wish to know the diagnosis, and questions regarding the subject's wish for his or her spouse to be told the diagnosis if the spouse had the disease. Reasons for wanting or not wanting to be told the diagnosis were also explored. The questionnaire is available from the authors.

Data were analyzed by descriptive statistics. Comparisons of categorical variables were analyzed by Fisher Exact tests.

## RESULTS

Of the 237 subjects who were sent questionnaires, 27% (n = 64) did not respond, 7% (n = 17) refused to complete the survey but returned it with a reason for the refusal, and 65.8% (n = 156) completed the survey. Reasons the 17 subjects gave for refusing to complete the returned survey included the following statements: "The matter should be kept between family and patients," "It

would upset me too much," "It would bother me," "This is too personal a decision to be made with too many variables and [can] only be made at the time of the event," "As a doctor, I don't have a patient viewpoint," "This is in poor taste - is upsetting to residents," "Not physically able," "I believe a physician/surgeon should be absolutely frank with a patient..., when my wife was in her late forties, she developed cancer and was terminal. The doctor advised against telling her. I didn't, and the results were horrifying," "My wife already has Alzheimer's and is incapable of participation," and "I don't have the time." No comment was made by seven subjects.

Demographics of the sample are shown in Table 1. In response to the question, "Has a relative or close friend of yours had Alzheimer's disease or a similar type illness with loss of memory?", 48.7% (n = 76) responded yes, and 51.3% (n = 80) responded no. By comparison, 79.5% (n = 124) answered yes when asked the same of cancer.

When asked whether the subjects themselves would want to know if they were diagnosed with AD, the majority (n = 124, 79.5%) responded they would want to know, 10.9% (n = 17) would *not* want to know, and 9.6% (n = 15) were "not sure." Reasons subjects gave for wanting to know are shown in Table 2. Other reasons (0.8%, n = 1) included, "To understand what is happening to me," "To be prepared spiritually," "To research ways to slow the disease down," "To settle spiritual matters," "To find out as much as I could about Alzheimer's disease -- not knowing would be more frightening than knowing." The majority (n = 105, 84.7%) gave three or more reasons for wanting to be told.

Of the 17 subjects who responded that they would *not* want to be told, reasons included "would be too upset," (n = 8, 47.1%) and "no cure anyway," (n = 16, 94.1%). "Other" reasons included (5.9%, n = 1) "Destroys hope, and positive thinking destroyed," "It would not help me to know. It would be

## Attitudes on being told the diagnosis

Table 1. Demographics of Study Sample

	Number	Percent
Mean age: 79.7 +/- 6.9 years		
Gender		
Female	96	61.5
Male	54	34.6
No answer	6	3.8
Race		
White	145	92.9
No answer	11	7.1
Religion		
Protestant	118	75.6
Catholic	14	9
Jewish	4	2.6
Other	2	1.3
No answer	18	11.5
Marital status		
Currently married	84	53.8
Not married/widowed	71	45.5
No answer	1	0.6

Table 2. Reasons Subjects Would Want to Know Diagnosis

	Alzheimer's Disease (n = 124) n (%)	Terminal Cancer (n = 143) n (%)
To do advance planning	122 (98.4)	132 (92.3)
To get a second opinion	91 (73.4)	106 (74.1)
To do financial planning	105 (84.7)	108 (75.5)
To settle "family matters"	95 (76.6)	107 (74.8)
To travel/vacation	35 (28.2)	37 (23.7)
Other includes:	9 (7.2)	30 (21)
To consider suicide while able	4 (3.2)	3 (2.1)
Other	5 (0.8)	27 (0.6)

depressing and might make me more difficult for others to take care of."

Subjects were then asked if their spouse had Alzheimer's disease, would they want their spouse to be told the diagnosis. Because not all subjects were currently married, only some subjects (n = 105) answered this question. Only 69 (n = 65.7%) would want their spouse told, which was significantly less (P = .008, 2-tail Fisher exact test) than the number of subjects who themselves would want to know. Only three subjects wrote comments to explain why. One subject wrote her husband was diagnosed with AD but was not told, and she thought that was best. "He would have become very depressed, and what normal life he had left would have been altered to the point we would have had no marriage." Another stated her husband 'has bipolar problems and the news might bring on a depression," and the third wrote, "by the time I was sure, he would not have understood."

Comparing subjects' responses regarding Alzheimer's disease to those about terminal cancer revealed a significant greater number of subjects would want to be told if they had terminal cancer (n = 143, 91.7%; P <= .001, Fisher exact test) than would want to be told if they had AD (n = 124, 79.5%). As with Alzheimer's disease, significantly fewer subjects would want their spouse told if the spouse had terminal cancer (n = 77, 80.2%, P < .001, Fisher exact test). Subjects' reasons for wanting to know the diagnosis of terminal cancer

are shown in Table 2. There were no significant differences between the reasons given for wanting to know of terminal cancer compared with AD.

No variables distinguished the groups who did or did not want to know the diagnosis, including prior personal experience with family or close friends with either illness.

### DISCUSSION

In this study, the attitudes of older people regarding "truth-telling" in Alzheimer's disease and terminal cancer were examined, and they revealed that a majority would want to be informed of both diseases, but significantly fewer would want to be told if the diagnosis were Alzheimer's disease. Despite the thoughtful written comments of the subjects, no clear reason to explain this difference emerges. It is possible that AD is viewed as a less treatable, or more hopeless, disease. As well, the inevitable deterioration of the mind in AD may play a role. The population studied was one with a relatively large personal experience with both Alzheimer's disease and cancer; the effect of these experiences or attitudes is unknown, but they may also play a role.

One unexpected, but very interesting, finding was that subjects were significantly less likely to want their spouse to know if the spouse had the illness. Approximately 33%

would *not* want their spouse told if the spouse had AD. This may raise difficult ethical issues for the physician. For example, families may bring in a patient but tell the physician, "I think he/she may have Alzheimer's disease, but if he does, please don't tell him." This study helps document that this attitude is common and may prepare the physician in dealing with this issue.

Reasons cited for wanting to be told the diagnosis were numerous and thoughtful. An unexpected response from several subjects for both illnesses was to consider suicide.. "while still able." Although few subjects indicated this as a reason to know, it is an important clinical reminder that such a diagnosis may be devastating to individual patients. Care should be taken to evaluate individual patients in their understanding and reaction to such news. Close follow-up, with psychiatric assessment when indicated, should be provided for such patients.

As clinicians who evaluate and treat Alzheimer's disease patients, the results of this survey support our view to inform patients of their diagnoses, to the extent that they are still able to understand. It is well recognized, however, that each case is unique and requires clinical judgment as to how much and what details of the illness the patient should be told. Knowing a patient well, and asking their preference in what, how much, and who should be told, regarding a diagnosis, is probably the best policy. Our study indicates there is no other way of knowing in advance who will and who will not want to know.

This study has several limitations. First, the population studied was largely white and Protestant and was financially able to live in a retirement community. Thus, results may not be generalizable to all older populations. A similar study in a different population is currently planned. In addition, only 65.8% of the sample completed the questionnaire; thus our results may have a self-selection bias. We do know, however, that the demographics of the retirement community resembles closely that of our sample. In addition, we did not determine whether the subjects themselves had been diagnosed with either AD or cancer, which may have influenced subject' responses. As well, the vignettes describe only one scenario, and it is recognized that

attitudes may vary depending upon the stage and severity of the disease. Finally, results of this questionnaire demonstrate subjects' current thinking about this issue. If the situation actually arose, different responses might occur. Despite these limitations, we believe the study is useful because it is one of only two studies examining attitudes toward being told the diagnosis of AD and the only study examining attitudes of older subjects toward being told about a diagnosis of AD. The comparison of AD with another condition (terminal cancer) allows some differentiation between the attitudes toward any "bad" diagnosis, and attitudes of AD in particular, a comparison that was not made in the previous study. In addition, it is the only study that examines attitudes about informing a spouse that he/she has a diagnosis of AD. This information may be useful for clinicians and may provide some initial data for further research into this issue.

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# After the Diagnosis

## Supporting Alzheimer's patients and their families

Richard J. Ham, MD

### PREVIEW

When the words "Alzheimer's disease" are first used regarding a patient with increasing memory and judgment problems, the person involved and his or her family members usually leave the office with sinking hearts. However, Dr Ham believes that using the term is important, because it gives structure to management and can be the impetus to seek information about the disease and learn about local support organizations. Clarifying the diagnosis is but the first of many ways that primary care physicians can assist families in deciding about home care, intensity of treatment, and long-term placement.

Physicians have a strong leadership role in their patients' care. In patients with Alzheimer's disease, this role should extend far beyond the usual medical decisions into emotional, ethical, and fiscal considerations. For example, educating caregivers in methods of coping with behavioral, cognitive, and physical ramifications of the disease benefits all concerned. Guidance to support services, including legal and fiscal resources as well as nutrition and home care, can relieve worry and frustration. And perhaps the most difficult but essential part of the physician's role is to provide information and advice regarding advance directives, long-term placement, and hospice care.

### Assessing the patient and the situation

If properly carried out, the diagnostic process in Alzheimer's disease forms the basis for future treatment. During patient assessment, all potential contributory factors should be sought, including medical conditions and use of medications. Physical examination should be comprehensive, with emphasis on functionality. Medical factors (eg, hearing loss, reduced mobility from arthritis, bowel and bladder problems) are often regarded by patients and family as part of normal aging, but they contribute greatly to the morbidity of dementia.

### Richard J. Ham, MD

Dr Ham holds the Distinguished Chair in Geriatric Medicine, Program in Geriatrics, Department of Medicine, State University of New York Health Science Center at Syracuse.

Correspondence: Richard J. Ham, MD, Program in Geriatrics, State University of New York Health Science Center at Syracuse, 750 E Adams St, Syracuse, NY 13210. E-mail: hamr@mailbox.hscsyr.edu.

### Involving the family

Thorough evaluation should involve issues surrounding the family and the environment. Few physicians can make home visits, but information can be gained from someone who does visit the home. Appropriateness of the environment, access to acute services, and the patient's daily function and alcohol and nutrition habits should be ascertained.

Methods used to establish the diagnosis can communicate the principles of management. For example, families need to know that their input is central to diagnosis and that after the diagnosis is established, they are central to treatment. Many physicians hesitate to give progressive dementia a name, but when criteria for dementia of Alzheimer's type are established, the term "Alzheimer's disease" should be used. Once given the diagnosis, patients and families often research the disease at libraries, look for a local Alzheimer's association in the phone book, and begin finding the support they will need.

**With education, families come to understand that patients with Alzheimer's disease truly *cannot* rather than *will not* function in certain ways.**

**Educating the family**

Many people immediately equate Alzheimer's disease with the worst form of dementia possible. They should be told that it is simply a specific diagnosis--one that accounts for the vast majority of progressive dementias in old age. Naming the disease gives structure and dignity to management. With instruction, families usually stop blaming the patient and assuming that he or she has control and is just being willful. Instead, they come to understand that patients truly *cannot* rather than *will not* function in certain ways.

Families should be given educational opportunities that are appropriate to their needs. Some seek information on their own, and others require direct instruction. Some want to know the whole picture, whereas others prefer to wait and see how the disease progresses. Three important issues should be noted:

- Media accounts tend to emphasize the suffering that Alzheimer's disease causes and often give the impression that progression is rapid. In fact, the course is usually prolonged, and a reasonable quality of life often can be enjoyed during much of it.
- Not every patient has every problem that has been described with the disease; some have a remarkably benign course.
- Many troublesome symptoms resolve with time. For example, patients do stop wandering, and eventually they will not miss the inability to drive. The agony that patients feel in early disease while they still have insight into the future will resolve as cognition declines.

**Disease stages and specific concerns**

There is great variation among patients in regard to progression of the key features of Alzheimer's disease and resulting limitations.

Patients who have visuospatial problems early in the disease course must give up driving early. (For others, driving is permitted, provided someone rides along who can observe visuospatial capabilities and take over if necessary.) Aphasia causes specific communication difficulties and may be associated with rapid progression if it occurs early. However, it is memory loss and the inability to use good judgment and make decisions (and the consequent dangers) that dominate early symptomology.

Measurement of cognition with use of the Mini-Mental State Examination can be helpful in determining disease progression (although results are not absolute, since education or impairment can influence the score on this culturally specific test). Patients' level of function can be characterized by formally recording the activities they can accomplish. For example, instrumental activities of daily living (IADLs) require interaction with the environment and are necessary for independent function. Among them are traveling, shopping, doing housework, handling money, preparing meals, and making telephone calls. Skills required for personal care (ADLs) are bathing, dressing, grooming, use of the toilet, self-feeding, and transferring or walking.

**Mild dementia**

Patients with mild dementia usually have a Mini-Mental State Examination score in the 20s (above 26 usually is considered normal). In general, they are capable of independent living, although they may exhibit challenging behaviors, particularly over taking medications, and need help with complex tasks, such as balancing the budget and planning meals. Simple reminder techniques (notice boards, medication calendars, daily pill dispensers, phone calls from family) can be a great help. When the ability to handle complex tasks begins to decline, they should be taken over quietly and carefully.

At this stage, advance directives or a living will should be constructed and a healthcare proxy appointed.

### **Practical tips on managing behavioral features of Alzheimer's disease**

- Repetitiveness. Caused in part by memory loss but also by lack of self-confidence, a patient's repetitiveness can sometimes be helped by giving a decisive answer and then distracting him or her. Caregivers may need to withdraw from the room for a moment and return armed with a new subject or activity.
- Lack of motivation. Indecisiveness and the feeling of being overwhelmed result in a loss of motivation, which can be mistaken for depression (and may also be a feature of it). Caregivers should organize fulfilling activities, which often means starting a project so the patient can complete it.
- Personality changes. Family members often remark, "This is not the person I've always known." Behaviors unrepresentative of the patient's previous personality, such as disinhibition or inappropriate sexuality are very difficult for family members to accept. Family members must be counseled, sometimes by a professional therapist, that their loved one is ill and is not choosing behaviors or directing them at a specific target. A sense of humor is the best protection but, unfortunately, this cannot be prescribed. Tranquilizers are of little help in modifying personality changes.
- Communication difficulties. From the early stages of Alzheimer's disease, patients have more trouble expressing themselves than understanding others. Comprehension may be better preserved than is apparent, so discussions about a patient should not take place in front of him or her. In some cases, impaired hearing or concentration is the cause of communication problems.
- Speech impairment. The expressive aphasia of early disease ultimately becomes sensory aphasia. Formal speech therapy is not usually indicated. Rather, to reduce frustration and increase function, family members should be encouraged to "fill in" for the patient.

- Wandering. Getting lost is a familiar problem in patients with Alzheimer's disease, so participation in the Safe-Return program is a good idea from the early stages. The patient wears a bracelet engraved with a toll-free number and 4-digit code. The number can be called from anywhere in North America to identify the patient and find out who to contact. Registration in the program can be completed through the local Alzheimer's Association or by calling 1-800-272-3900

- Emotionality. Dysphoric apprehension may be better preserved, but sometimes can be overcome with distraction. Dwelling on and weeping over memories may be a feature of depression.

- Aggressive outbursts. These are not only frightening, they can be dangerous. Sometimes they occur when the patient is overwhelmed by a situation (eg, a visit to the emergency department). Families should be taught to avoid events that are likely to induce "catastrophic reactions," to reduce the number of experiences taking place at one time, and to ensure guidance by a familiar companion in busy situations. If aggressive outbursts are part of a generally agitated behavioral pattern or occur often, low doses of an antipsychotic agent or minor tranquilizer may help.

### **Moderate dementia**

Patients with moderate dementia usually have a Mini-Mental State Examination score in the

**Preservation of long-term memory through reminiscing, viewing photos, and visiting familiar places can be rewarding to Alzheimer's patients and their families.**

teens. They are often capable of independent living but require significant help with daily tasks. They are probably unable to cope with change or with an unfamiliar environment. Formal day-care is usually beneficial as both therapy for the patient and respite for the

caregiver. Attendance is often arranged for 3 to 5 days a week, but even 1 or 2 days is useful. Nutrition and wandering are particular concerns during this stage.

### **Severe dementia**

Patients with severe dementia usually have a Mini-Mental State Examination score of 10 or below. They need help with ordinary daily tasks and are usually undergoing physiologic decline, including loss of bowel and bladder control and mobility problems. Physical decline leads to severe dependency and, ultimately, death. Care in a supervised setting often becomes necessary at this stage.

### **Memory loss**

Memory loss is usually the first and most persistent sign of Alzheimer's disease and is required in the definition of dementia. Initially, short-term recall is affected most severely, but ultimately, long-term memory becomes impaired and even familiar people and things lose their significance.

During the early phases, imaginative care can greatly reduce the impact of memory loss. Perhaps the most useful tool during the early stage, when awareness and insight are still intact, is a notepad on which the patient can jot down information for future reference. Use of the reminder techniques mentioned earlier is another simple method that can minimize frustration and dysfunction.

Preservation of long-term memory during the early and middle phases of dementia can be therapeutic. It is well recognized that reminiscing can be rewarding and fulfilling, increase the patient's quality of life, validate their experiences, and increase their sense of worth and self. Since patients lack organizational and conceptual skills even early in the course of dementia, the caregiver should organize and prompt discussions about family photos, videotapes, and music that evoke memories as well as plan activities in familiar places. These techniques help improve family relationships, thus rewarding both the caregiver and the patient. Videotapes of familiar old television shows and favorite movies are often

comforting as well.

### **Depression**

Depression, especially in the elderly, can cause cognitive impairment sufficient to give the impression of dementia (ie, the dementia syndrome of depression). Depression can also coexist with early dementia, but signs are easily overlooked as caregivers deal with all the other problems of a dementia patient.

Concurrent depression in patients with Alzheimer's disease can cause a sudden decrease in cognitive capability or an increase in somatic awareness, bringing complaints of aches and pains and other symptoms. Some patients have classic vegetative symptoms.

Depression occurring with dementia can be successfully treated with medication, as will be discussed. Left untreated, it results in malconditioning that can have permanent effects. Electroconvulsive therapy has been used in profoundly depressed dementia patients

**Faced with a tray full of foods, Alzheimer's patients may choose none. Given a smaller selection, they are more likely to eat.**

and is no more unsafe than in any other patient. It should be considered in patients who are so depressed they are in imminent danger (eg, because they are not eating).

### **Nutrition**

Maintaining good nutrition is a challenge at all stages of dementia. In early disease, poor visuospatial skills and diminished judgment can cause problems. For example, faced with a tray full of foods, patients may choose none. However, given foods one by one or in smaller portions (preferably in a form that is easy to handle), patients are more likely to eat.

Some patients eat better when offered food at frequent intervals or when finger foods and fluids are conveniently available. Some patients eat better in social settings; however, distractions should be minimized. For patients who like to eat

out, going to a familiar restaurant at a quiet time and telling the waiter about special needs are helpful.

Nutritional supplementation is vital. Canned, flavored, nutritionally complete supplements are widely available. They can totally replace traditional meals but initially are given between meals.

As dementia progresses, patients become unable to organize meals and to shop. Meals On Wheels, senior-citizen programs, and other social services can help make meals available. In late dementia, patients lose the ability to feed themselves. Caregivers should know the established techniques for spoon-feeding (Table 1), because success with this process can postpone the need to use a feeding tube. A dietitian and a speech therapist (for swallowing problems) are essential for optimal continuation of oral feeding. Percutaneous endoscopic gastrostomy tubes have revolutionized long-term nutritional maintenance. However, ethical issues are involved in their use: Is it right to maintain nutrition in a person in the final stage of dementia? It has been shown that adequate nutrition and hydration are not "comfort measures"; that is, patients can be perfectly comfortable (if oral care is maintained), even if they are undernourished and underhydrated. An informed decision by the patient or the family to not use such intervention may be in the patient's best interest, as discussed again later.

### **Practical tips on managing cognitive features of Alzheimer's disease**

- Indecisiveness. Reducing the number of choices available can aid patients. For example, choosing foods and clothing become overwhelming activities. Caregivers should avoid asking for a decision such as "What do you want for lunch?", but rather, "Let's have lunch".
- Disorientation. At first, only new environments are bewildering, but later even the home becomes a confusing place. Providing cues (eg, "Here is your room, at the end of the hall") often helps.

Since relocation usually causes disorientation, familiar items should be brought along during a temporary hospital stay. Physicians, nurses and caregivers should make an effort to maintain one-on-one eye contact when possible.

- Hallucinations. Visual and auditory hallucinations may not be distressing unless the patient starts being directed or frightened by them. If treatment is necessary because hallucinations interfere with the patient's function or add to agitation, antipsychotic agents are the first choice. Hallucinations may derive from misinterpretation of actual events and objects. A careful search for the initiating event may help, but once delusional systems become established, use of antipsychotic drugs is often indicated. Families should be aware that these phenomenon are real to the patient, and confrontation typically ends in an argument. Neither should the families go along with misapprehension since this will reinforce the hallucinatory or delusional pattern. Redirection and distraction are useful strategies.

**Dementia patients decondition rapidly and are liable to lose a function that is taken away for more than a few days.**

### **Hospitalization**

Hospitalization is hazardous for patients with dementia. A family member should be encouraged to accompany the patient to reduce anxiety and restlessness, and hospital staff members should be trained in reorientation techniques, attention to skin care, and maintenance of mobility skills. Dementia patients decondition rapidly and lose daily-living skills. Taking away any function for more than a few days is liable to result in loss of that capability. For example, patients who feed themselves must be encouraged to continue to do so during hospitalization. Room lights should be left on to lessen fear and disorientation.

## Deciding how to use drug therapy

Considerable publicity surrounds every advance that might benefit patients with Alzheimer's disease. At the time of this writing, estrogen is in the news because it may have a protective role against the disease in women and possibly in men. Nonsteroidal anti-inflammatory drugs are also of interest. Their anti-inflammatory action may reduce neuronal damage around the lesions of Alzheimer's disease, and there is some evidence that Alzheimer's patients who are taking these drugs have a slower decline in cognition.

A recently published trial confirmed that antioxidant therapy with vitamin E can postpone functional decline in ambulatory patients with moderately severe Alzheimer's disease. Results have been widely interpreted as implying that vitamin E may have a preventive role. The study also involved selegiline hydrochloride (Eldepryl) and confirmed that it, too, could postpone functional change. However, the two agents given together had less effect than either given alone; for economic and safety reasons, most investigators believe that vitamin E would be the reasonable choice between the two.

Only two medications are approved for specific treatment of Alzheimer's disease: the cholinesterase inhibitors described in the following text. Physicians must take care to not overlook medical problems that are even more pharmacologically treatable (eg, concurrent depression or pain, hearing loss).

### Cholinesterase inhibitors

Tacrine hydrochloride (Cognex) and donepezil (Aricept) are the approved anti-Alzheimer's disease drugs. Both increase the quantity of the neurotransmitter acetylcholine, which is known to be reduced in Alzheimer's disease. This reduction is directly related to the degree of cognitive impairment.

I believe that patients with mild to moderate dementia of the Alzheimer's type should be offered a therapeutic trial with one of these drugs. Tacrine must be taken four times daily, which is difficult for patients with memory impairment. Doses must be increased slowly, and the usual therapeutic level is not reached for

6 months. Laboratory testing is required every 2 weeks for about the first 8 months of therapy to screen for liver damage (which is rare). Donepezil is newer, so less clinical experience is available. However, it is taken once daily (so compliance is good), it does not require laboratory testing, and it appears to be more effective and better tolerated than tacrine.

In treatment of Alzheimer's disease, achieving a plateau in deterioration of cognitive function is considered success. Therefore, judging whether a given patient is benefiting from therapy requires knowledge of the speed of decline prior to treatment as well as considerable clinical judgment, supported in part by serial mental-status testing.

## In treatment of Alzheimer's disease, achieving a plateau in deterioration of cognitive function is a triumph.

### Psychotropic agents

Many families have inappropriately strong negative feelings about use of psychotropic medications. However, these agents can be extremely valuable and should be tried when behavioral and environmental approaches do not succeed. A therapeutic trial of a psychotropic agent may be beneficial in patients who are very agitated much of the time, hallucinatory, or delusional to the point of being disturbed or frightened; patients who are experiencing "sundowning" (ie, are nearly psychotic in the evening and at night) and are therefore a management problem because they are not sleeping; or patients who often have aggressive outbursts. The rule with psychotropic agents is to start doses low and increase until effectiveness is noted. Starting at a low dose risks disinhibition, which makes patients seem worse at first. In such cases, the dose should be *increased*, not discontinued prematurely, as is often done because of physician nervousness and family pressure. These medications almost never cause permanent effects, although tardive dyskinesia can be a long-term sequela. Discontinuation of these drugs usually brings

resolution of the well-recognized side effects, such as extrapyramidal syndrome and dystonic reactions (eg, akathisia). The two anti-psychotic agents used most widely in Alzheimer's disease are thioridazine hydrochloride (Mellaril) and haloperidol (Haldol). Thioridazine cannot be universally recommended because of its strong sedating and anticholinergic effects. Haloperidol is regarded by many as a "rogue drug" because of its overuse in the past. In fact, it is a good anti-psychotic agent, but it can produce extrapyramidal syndrome.

Risperidone (Risperdal) is a new drug with a better side-effect profile than the older agents, but it is much more expensive. I have found it to be extremely useful, since it fits nicely into the "therapeutic window" between calming agitated behavior and causing sedation.

### **Tranquilizers**

Minor tranquilizers also have a place in treatment of Alzheimer's disease. Lorazepam (Ativan) is probably the most recommended short-term benzodiazepine and can usually produce sedation, even in acute situations. Occasionally, it is a useful alternative to anti-psychotic agents for severe agitation.

### **Sedatives**

Patients who are awake much of the night can be a major problem for caregivers. Simple remedies, such as use of melatonin (obtainable at health-food stores) or a short-acting sedative, such as zolpidem tartrate (Ambien), may help insomnia. If stronger sedation is required, a low dose of an antipsychotic agent is preferable to a longer-acting benzodiazepine, which often has lingering effects the day after ingestion. Diphenhydramine hydro-chloride, available over the counter (eg, Benadryl, Tylenol PM), can help but may increase confusion because of its anticholinergic side effects.

### **Antidepressants**

When two or more of the following signs persist for more than 2 weeks, therapy with a nonanticholinergic antidepressant (eg, a selective serotonin reuptake inhibitor) should be tried:

- New-onset sleep disturbance
- Appetite change
- Constipation
- Diurnal mood variation
- Persistent sadness

The relatively mild antidepressant trazodone hydrochloride (Desyrel) is widely used in Alzheimer's disease for its tranquilizing properties, although it is quite likely to cause orthostatic hypotension. Therefore, it is a reasonable choice in a patient who is depressed and also agitated. However, using two different medications to achieve the two different effects is often preferable so that benefits and side effects of each can be judged separately.

The phenothiazine-related antidepressant amoxapine (Asendin) is sometimes useful late in the disease in very depressed patients who are withdrawn yet clearly in a state of despair.

### **Practical tips on managing physical problems in Alzheimer's disease**

- Mobility and balance problems. Regular walking and reconditioning can, to some extent, slow mobility problems and maintain balance skills. Impulsivity or lack of attention is the cause of many falls. Keeping the environment well lit and uncluttered is important.
- Musculoskeletal stiffness. As the disease progresses, the legs in particular become stiff. Exercise can counter the problem somewhat. Contributory conditions, such as osteoarthritis, should be sought and treated.
- Sleep disturbances. These problems are very stressful for caregivers and, unfortunately, are common. Use of hypnotics is undesirable since this can produce other problems, so the initial approach is to decrease activity during the day. Patients should be discouraged from taking naps during the day so that their period of needed sleep coincides with that of the family. At bedtime, leaving some lights on (because darkness is frightening to these patients) and playing calming, familiar music to create an atmosphere of warmth and security also helps.
- Dysphagia. A common outcome of any

**Table 1.** Practical hints for feeding patients with late dementia

Problem	Interventions
Poor attention or concentration	Talk through steps, place utensils in patient's hand, place food where patient can see it
Combative or throws food	Present one food at a time, sit on patient's nondominant side, offer rewards, use unbreakable dishes held in place with suction cups
Constant chewing	Feed soft foods in small bites, remind patient to stop chewing
Distracted or indecisive	Keep environment consistent, diminish distractions, limit choices, present one food at a time
Forgets to swallow	Stroke larynx upward, tell patient to swallow, feel the swallow before offering next bite
Restlessness	Assure exercise before meals, sit beside patient, offer finger foods, use covered and spouted cups
Cannot use objects correctly	Make eating a series of simple steps, use verbal cues, give finger foods, limit number of utensils and cups
Bites utensils	Use vinyl-coated spoons, do not insert utensils fully into patient's mouth, massage arm and leg muscles to promote relaxation of bite, tell patient not to bite
Cannot or will not chew	Check if dentures fit, place food on alternate sides of mouth between gum and cheek, remind patient to chew
Does not remove food from utensil	Place small amount of food on front of spoon, tell patient to close lips, withdraw spoon as lips begin to close; use "pusher" spoon
Keeps food in mouth	Cool spoon with ice between bites, press top of patient's head with open palm to trigger swallowing, vary texture of food
Keeps mouth open, food falls out	Use spouted cup, blot patient's lips, do lip-closure exercises (eg, with a Popsicle)

Adapted from Ham RJ. Confusion, dementia and delirium. In: Ham R J, Sloane PD, eds. Primary care geriatrics: a case-based approach. 3d ed. St Louis: Mosby, 1997.

neurologic condition, dysphagia is sometimes a direct result of dementia. Patients with early-onset dysphagia may require long-term nutritional support, such as a feeding tube. The possibility that dysphagia is due to a new stroke should be considered, since such dysphagia may resolve in time.

- Urinary incontinence. This common problem can also be the direct result of dementia. Patients may respond to behavior management in the form of reminders and regular trips to the toilet. Ultimately, diapering (*not* catheterization) may become necessary. A proper workup for other factors (eg, urinary tract infection) should be carried out.
- Fecal incontinence. Regular raps to the toilet, especially after a short amount of exercise within 30 minutes after breakfast or lunch, can help avoid distressing accidents.

### Planning long-term placement

Although care at home can work even in later stages of dementia, and it avoids the trauma of reinstitution, family members or friends must be able and willing to devote considerable time to care. In addition, families are responsible for most of the costs involved in providing 24-hour supervision.

Most often with dementia, the need for more supervision becomes clear over time, and there may be a period of some risk for patients living at home. Patients often refuse placement, even though they would clearly benefit from it, and may not welcome the "interference" of family members trying to ensure their safety and good nutrition.

Planning placement in a long-term facility before it becomes an urgent need can ease the transition. Physicians should ensure that the family has considered different options and the financial requirements of each. Some estate planning techniques focus on making patients eligible for Medicaid as soon as possible, a practice that is ethically questionable, since Medicaid was designed to pay for the authentically poor, not the artificially rendered poor.

One type of facility is an adult home (sometimes called a board-and-care facility). This type

of living situation is designed for patients who can prepare simple meals for themselves, but they can come to a common dining area if they wish. Residents in adult homes are able to take care of at least some of their own personal needs.

If skilled nursing care becomes necessary, the physician should assist the family in making appropriate choices. The physician's main responsibility is to be aware of the quality and philosophy of local resources. Too often, an Alzheimer's patient sustains an illness or injury (eg, hip fracture), is hospitalized, and then moves fairly directly into a skilled-care facility. Patients do not necessarily require placement in an Alzheimer's-specific unit, although some such units do offer decidedly superior programs (eg, appropriate environment, efforts toward retaining long-term memory). In some cases, patients do better in a mixed environment.

### Terminal care

In the late stage of Alzheimer's disease, control of physiologic functions is lost (urinary and sometimes bowel incontinence) and contractures and skin problems develop. Increasingly, hospices are involved in the final stages of the illness, because they have precisely the expertise and resources necessary to help. The physician must confirm that a patient has only 6 months or less to live before Medicare pays for hospice care. Efforts have been made to define criteria for such a prognosis in patients with progressive dementia such as Alzheimer's disease (Table 2).

If a hospice is not available, appropriate palliative techniques should be used, and counseling and support of the grieving family members should be organized. Palliative measures should include careful oral care, uncomplicated approaches to intestinal obstruction and concurrent infection, control of respiratory distress, and relief of pain. Morphine should be given regularly in escalating doses to keep the patient comfortable, *not* just when pain or distress breaks through.

**Table 2. Feature of terminal stages of Alzheimer's disease**

Limited vocabulary (six words or less)  
Absence of smiling  
Inability to walk without substantial assistance  
Inability to sit up independently  
Difficulty eating or swallowing  
Recent weight loss  
Decreased consciousness or coma  
Bowel or urinary incontinence  
Recurrent respiratory or urinary tract infections  
Inability to hold up head or track objects with eyes

*Adapted from Ham RJ. Confusion, dementia and delirium. In: Ham R J, Soane PD, eds. Primary care geriatrics: a case-based approach. 3rd ed. St Louis: Mosby, 1997.*

**Advance directives and ethical decision making**

Families and professionals need to realize that their role in nutritional and other determinations is to make decisions as the patient would have made them. The personal outlook and desires of these individuals should not enter into the decisions, although the clinician's judgment about the nearness of death should be considered.

The usual ethical rule is that pointless treatment or procedures that will not benefit the patient need not be carried out. Therefore, if the physician believes, for example, that insertion of a percutaneous endoscopic gastrostomy tube is pointless, the ethical medical decision to forgo tube placement can override even family desires. Of course, if the patient's expressed wish was to be maintained with tube feeding, that wish is to be honored. Many other issues concerning intensity of treatment come up as the end approaches or even earlier. For example, how intensely should concurrent illness be investigated and treated? Osier is reputed to have called pneumonia the "old man's friend," and it may well be so as a patient nears death. Not treating pneumonia and instead allowing it to quietly end the life of a patient who is dying anyway is perfectly reasonable, but all caregivers, nonprofessional as well as professional, need to be at ease with the decision.

To clarify decision making in the terminal stages of disease, patients and families should construct a living will or other advance directive early in the disease, clarifying wishes about resuscitation, artificial feeding, and intensity of treatment when the situation is hopeless. For example, documentation of the patient's wish to not be maintained on a feeding tube or respirator is vital when the time comes to make that decision. Appointing a healthcare proxy may be considered to address care needs when the patient can no longer contribute. Also, it may be best to establish a durable power of attorney so a trusted representative is available to look after financial affairs.

**Summary**

Expert management of progressive dementia stretches all the capabilities of the physician and of the healthcare system. For the physician, prescribing appropriate medication is certainly an essential role, as is involvement with social services and other health professionals to help patients and families make the best decisions related to use of resources and, sometimes, to placement in a care facility.

Physicians dealing with progressive dementia should remember the following basic principles:

- Care is best provided by a loosely organized team consisting of health professionals, nonprofessional healthcare providers, and the family (or a substitute for it).
- The overall objective of management is to prevent or delay functional decline.
- The patient's safety is an early and continuing concern.
- The environment, even when it is changed temporarily, must be appropriate to the patient's level of function.
- Coexistent disease (the presentation and management of which may be altered by cognitive impairment) must be diagnosed and treated promptly and efficiently.
- Advance directives and healthcare surrogates should be determined early, while the patient can still have input.

## Alzheimer's Disease

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# **Part 3**

## **Pathology**



# Structural Basis of the Cognitive Alterations in Alzheimer Disease

Robert D. Terry, Eliezer Masliah, and Lawrence A. Hansen

## Gross Changes in Alzheimer Disease

### Microscopic Lesions

Plaques, Tangles,  
Neuropil Threads, Amyloid Angiopathy, Hirano Bodies, Granulovacuolar Degeneration

### Neuronal Loss

### Synaptic Alterations

**Alzheimer Lesions in the Nondemented Elderly Diagnostic Criteria:** Sensitivity and Specificity

**The Causes of Dementia in Alzheimer Disease Acknowledgments**

### References

Alzheimer disease (AD) is only rarely seen before the age of 60, but its prevalence increases rapidly after that age such that by age 85 more than 40% of survivors may be affected. The pathology of AD, therefore, is additive to those cerebral changes that occur in normal aging. The latter are usually quite subtle with mild brain atrophy and perhaps a few plaques in the neocortex, and sometimes even a few tangles as well as plaques (vide infra) in the hippocampal and entorhinal areas. There have been many studies of neuronal populations as a function of aging, and as to the neocortex there seem to be two groups of results. The classic reports of Brody (1) found that there was a significant loss of neurons, especially the smaller ones, from the cortical gray matter. Others, including those by Haug (2) and by Terry et al. (3), reported an essentially unchanged total population of neurons with decreased numbers of pyramidal projection cells and increased numbers of smaller neurons in association cortex. They concluded that many large neocortical neurons atrophied so that they were counted among the smaller neurons. There is also a mild increase in immunocytochemically recognizable fibrous astroglia in the aging cortex (4).

Most investigations suggest that the dendritic arbor shrinks in the course of normal aging (5). Contrarily, however, Buell and Coleman (6) demonstrated in a Golgi study of the hippocampus that some neurons have expanded dendritic trees in the normal elderly. In view of the overall shrinkage of the cerebrum and narrowing of the cortical ribbon, it is difficult to accept that there is a widespread net growth of dendrites in normal aging, although some cells may show this sort of plasticity, which might even offer a restorative effect.

A recent analysis concerned the population density of neocortical synapses in normal aging (7). Utilizing confocal microscopy to quantify the number of anti-synaptophysin reactive presynaptic terminals in dorsal prefrontal cortex in 25 specimens between ages 19 and 95, Masliah et al. (7) found that there is a quite steady decline in synaptic population with a correlation coefficient ( $r$ ) of .66, significant ( $p$ ) at less than 0.001. If, as increasing numbers of investigators believe, synaptic loss is the immediate cause of dementia, it is theoretically possible that the loss of synapses in normal aging, extrapolated beyond the current lifespan, might lead to a dementing threshold at an advanced age in the absence of disease. If for example, a loss of 35% of the young adult synaptic number would cause dementia, then that threshold would be reached at the theoretical age of 115 years. A threshold of loss of 45% would not be reached until about 150

R. D. Terry, E. Masliah, L. A. Hansen: Departments of Neurosciences and of Pathology, University of California-San Diego, La Jolla, California 92093-0624.

years. The more immediate point is that because of the addition of age factors to disease, the elderly need lose fewer synapses through disease than do younger patients in order to reach a level of cortical damage sufficient to cause dementia.

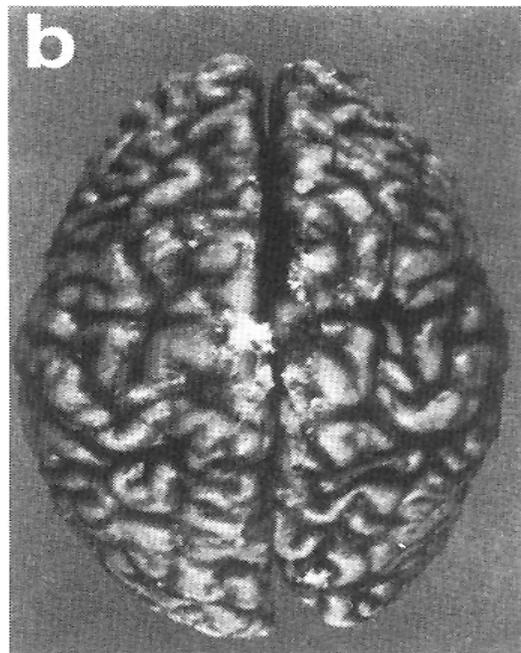
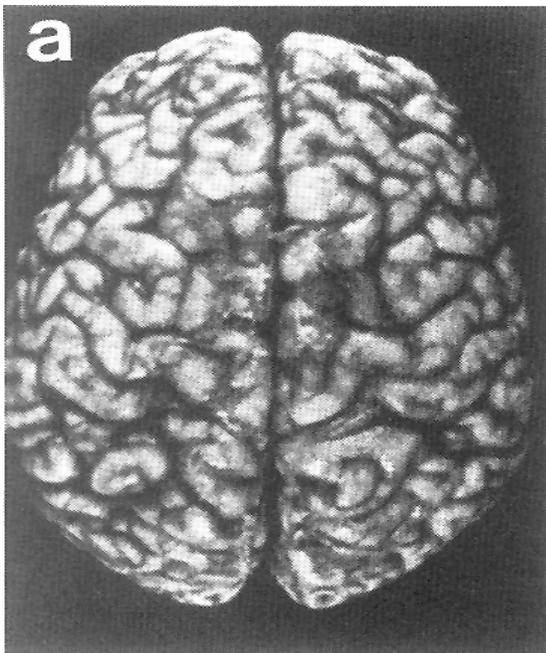
The two now classic lesions described by Alzheimer (8) in his first report of a presenile demented patient, the senile plaque and the neurofibrillary tangle, are those by which pathologists make the histologic diagnosis of Alzheimer disease. There is no question but that the average number of these lesions in hippocam-

pus, neocortex, and several other areas is significantly greater in the demented patients than

in normal controls. Since the time of his original reports, however, our understanding of these lesions has become more complex. In addition, other structural abnormalities and losses have been noted.

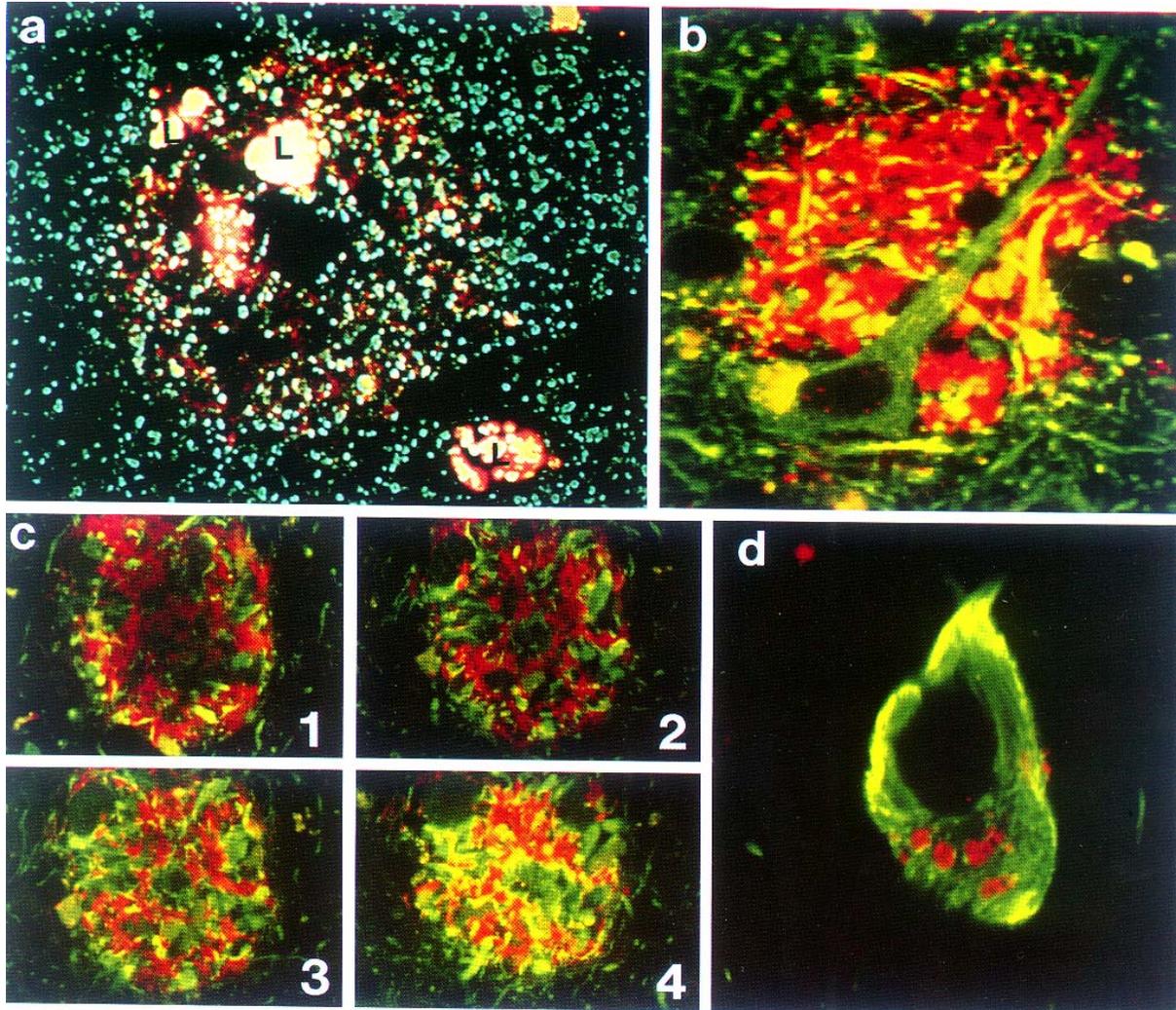
## GROSS CHANGES IN ALZHEIMER DISEASE

The leptomeninges over the convexity and especially near the midline are often mildly to moderately thickened (Fig. 1). This opacification parallels to some extent the degree of underlying cortical atrophy, but this is not always the case in that at times there can be quite intense disease with little or no apparent thickening of the leptomeninges. This thickening, to whatever degree, corresponds microscopically to a greater or lesser addition of fibroblasts and collagen to the meninges. Buried within the leptomeninges are vessels that are very often infiltrated with  $\beta$ -amyloid. It is often more prominent here in the meninges than in the parenchyma, but the appearance is very similar (vide infra). The amino acid sequence of the  $\beta$ -amyloid in the meninges is only very slightly different (near the amino terminal) from the parenchymal deposits (9) (Fig 1).



**FIG. 1.** Gross examination of the surface of the brain. (a) Normal brain. (b) Alzheimer diseased brain

displaying gill atrophy.



**FIG. 2.** Laser scanning confocal microscopy of the lesions in Alzheimer disease (AD). The images in green are labeled with a fluorescein isothiocyanate (FITC)-tagged secondary antibody and the ones in red are tagged with Texas red or CY5. (a) Diffuse plaque double labeled with an antibody against amyloid (*red*) and synaptophysin (*green*) shows that the loss in synaptic population is not different inside and outside the diffuse amyloid deposit. (L, autofluorescent lipofuscin). (b) Plaque double immunolabeled with an antibody against amyloid (*red*) and neurofilament (*green*) shows a neuron and its processes trapped in the midst of the amyloid mass. The neuron and neuritic structure (*green* and *yellow*) appear relatively preserved. © Serial step sections of a neuritic plaque double labeled with anti-amyloid (*red*) and anti-tau (*green*) displaying redistribution of neurites through the thickness of the plaque. (d) Several step sections of a tangle bearing neuron have been superimposed to show the distribution of the Golgi apparatus (*red*) and the abnormal fibers (*green* and *yellow*).

Shrinkage of the gyri is usually apparent, but not always so (Fig. 1). The weight of the brain in AD is most often between 1,000 and 1,100 grams, but varies from less than 900 to 1,400,

even in the presence of quite severe microscopic changes. The gill atrophy is most often apparent in the frontotemporal areas, but the parietal lobe is very often grossly involved. At the base of the

brain the shrinkage can be noted on the ventral surface of the temporal lobe, especially involving the parahippocampal gyrus. The widened sulci resulting from gray atrophy are also noticeable on the mesial surface of the hemisphere. Knife-edge gray atrophy is more common in Pick's disease than in AD. The paracentral gyri are less shrunken than those in frontotemporal areas, but not infrequently do display mild atrophy. No part of the cerebral cortex is uninvolved in the great majority of cases, but the occipital pole is often spared relative to other cortical areas. Occasionally, the gray atrophy is not diffuse, but rather may be asymmetric or even focal or lobar. Occasionally, a case of microscopically typical AD very closely resembles the gross frontotemporal atrophy of Pick's disease, even to the point of sparing the caudal half of the superior temporal gyrus. Sometimes, the cerebellar vermis also displays mild shrinkage, but this is probably the result of a nutritional deficiency rather than of AD itself.

The cranial nerves are normal except for the olfactory bulb and tract, which are very often significantly atrophied to the point of translucency. The arterial system is usually less atherosclerotic than one would expect in this age group. Amyloid infiltration of the meningeal vessels is not grossly apparent.

Sectioning the brain usually reveals certain gross changes in the moderate or more advanced cases of AD. The cortical ribbon may be mildly thinned, but this usually is not uniform. It may be more apparent in some regions than in others, and most often it is visible in the ventral temporal gyri. The cortex is well demarcated from the white matter, but there may be some gross alterations in the centrum semiovale such as fine granularity, slight softening, or even translucency. Small infarcts or lacunae undetected clinically may be noted, most often in the basal ganglia. The lateral ventricle often displays enlargement with rounding of its lateral angle. The enlargement is often greatest in the temporal horn because of the shrinkage of the amygdala and hippocampus. The basal ganglia are grossly intact with good preservation of the convex caudate nuclei. Shrinkage of caudate is

well known in Huntington's disease and less well known, but amply recorded, in Pick's disease; however, it is not seen in AD. The hippocampus as seen on cross sections is very commonly shrunken to about one-half of its normal width. The substantia nigra is usually normally pigmented, but may be slightly pale. When it is distinctly pale and tan, one usually finds that the case represents the Lewy body variant of AD or diffuse Lewy body disease (see chapter by Hansen). The locus coeruleus on the other hand is commonly very pale in AD, to the extent that it may even be difficult to find. The rostral portion of the locus coeruleus is more often damaged (10) than the whole nucleus, but this is difficult to discern without serial sections and microscopic studies.

### MICROSCOPIC LESIONS

#### Plaques

The two lesions that Alzheimer (8) identified in the first patient he described were the plaque and tangle. The average concentration of these lesions in the cortex and hippocampus is significantly greater in AD than in normal aging or in other disorders. However, some specimens from cognitively normal aged people have displayed a density of plaques that is well within the numerical limits for the diagnosis of AD (11). If the disease is to be diagnosed on the basis of the presence of both dementia and specifically altered brain structure, then these latter cases do not represent AD. Further confusion results from the finding that some demented patients have numerous plaques in the cortex without significant numbers of cortical tangles, which are either totally absent or very sparse (12). Such "plaque only" AD cases are often, but not invariably, accompanied by brain stem and neocortical Lewy bodies (see chapter by Hansen). Alzheimer disease without neocortical tangles is very unusual in patients younger than 70 years. The finding of many plaques without dementia may be accounted for on the basis of an unusually large neuronal and synaptic reserve as discussed by Katzman et al. (12), or by the newer notion that it is not plaques

that cause dementia but another even more subtle alteration (13) (vide infra).

These lesions have been called senile plaques for decades, but are found in the proscenium as well, although usually in small numbers (14). There are two major types--those with and those without abnormal neurites (Table 1). Those without neurites are called diffuse plaques (Fig. 2a,b; see color figure between pages 180 and 181) and have only minute wisps of formed filamentous amyloid as well nonstructured  $\beta$ -amyloid that is positive with silver stains as well as with thioflavin-S (Figs. 3a and 4). These diffuse plaques are found in some elderly normal persons and in AD. The neuritic plaques contain dense bundles of amyloid fibrils staining with thioflavin-S (Fig. 4) (9 nm in diameter) (Figs. 3, 5, and 6b,c) and dystrophic neurites of two major types (Fig. 2c). First there are fusiform neurites that mainly contain paired helical filaments and some dense laminated bodies (Fig. 7). The neurites of the second type are enlarged, bulbous structures that contain neurofilaments, laminated bodies, synaptic vesicles, mitochondria, and lysosomes (3,4) (Fig. 7). While abnormal neurites with paired helical filaments (PHF) are characteristically found in the plaques of AD, altered neurites without PHF are found both in plaques of AD and normal aged individuals. The abnormal neurites in the plaque contain amyloid precursor protein (15-18) (Fig. 8c), growth-associated protein (GAP43) (19,20), protein kinase C ( $\beta$ I) (21,22), tau (23) (Fig. 9a), ubi-quitin (24), brain spectrin (25), epidermal growth factor (EGF) receptor (26), neurofilaments (27) (Fig. 8a), synaptophysin (28-30) (Fig. 8a,b), and chromogranin, as well as a wide variety of neurotransmitters (e.g., substance P and acetylcholine) (31-34). The presence of GAP43 implies that at least some of the neurites are regenerative sprouts rather than simply degenerative swellings.

The amyloid core as well as the amyloid fibrils in the periphery of the mature plaque are immunoreactive with antibodies against  $\beta$ -amyloid (Fig. 6). However, recent studies have shown that both diffuse and mature plaques are also immunostained with antibodies against  $\alpha$ 1-

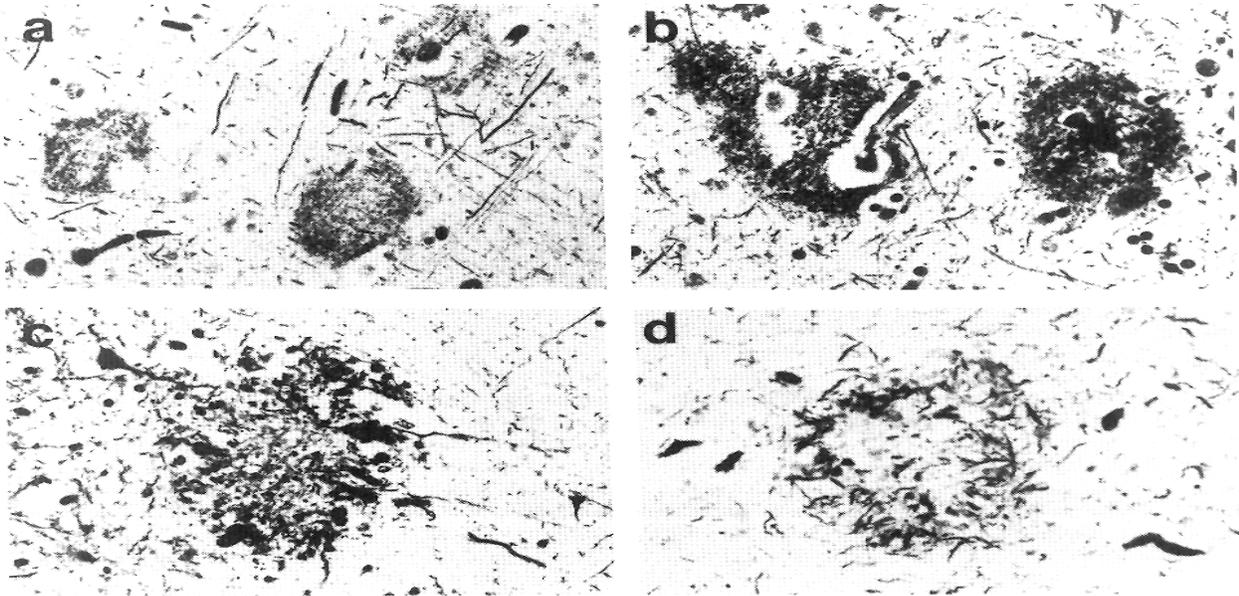
antichymotrypsin (A laCT) (35), protein kinase C (13II) (36,37), complement (38), apolipoprotein E (39), fibroblast growth factor (40), and sulfated glycosaminoglycans (41). Of all these components only AlaCT has been clearly shown to be an integral component of the amyloid fibrils (35). The other molecules are probably bound secondarily to the amyloid in the plaque.

In addition to the amyloid fibrils and the abnormal neurites, most of which are presynaptic (42), neuritic plaques are surrounded by proliferating astrocytes and by microglial cells (Fig. 5) (14). These latter phagocytic cells have been implicated in amyloidogenesis, the suggestion being that they process the amyloid precursor to form filamentous amyloid (14). Others have suggested that immune mechanisms contribute to the development of the mature plaque (43).

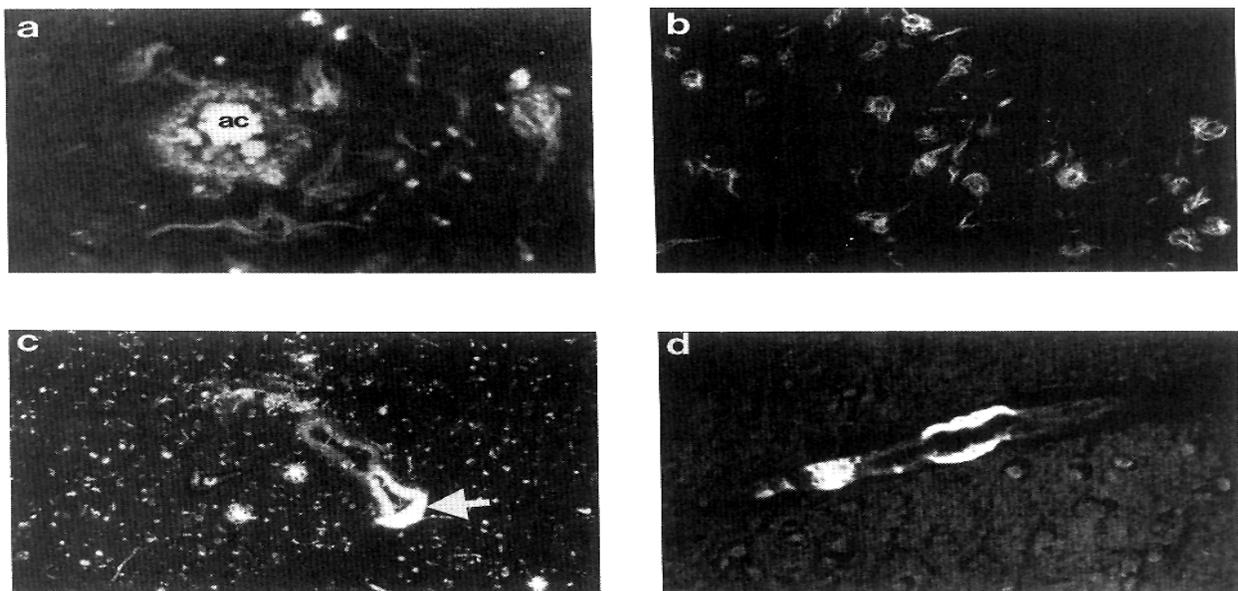
Many theories have been proposed as to the origin of the plaque. The best-known hypothesis contends that the neuritic plaque develops from a preceding diffuse plaque (44) that may have been present for many years. However, these diffuse plaques are also located not only where mature plaques are found, but also in cerebellar cortex and basal ganglia where the mature neuritic forms are almost never present. So there must be, in addition to the presence of the diffuse lesion, micro-environmental factors in the development of neuritic plaques.

TABLE 1. *Senile plaques*

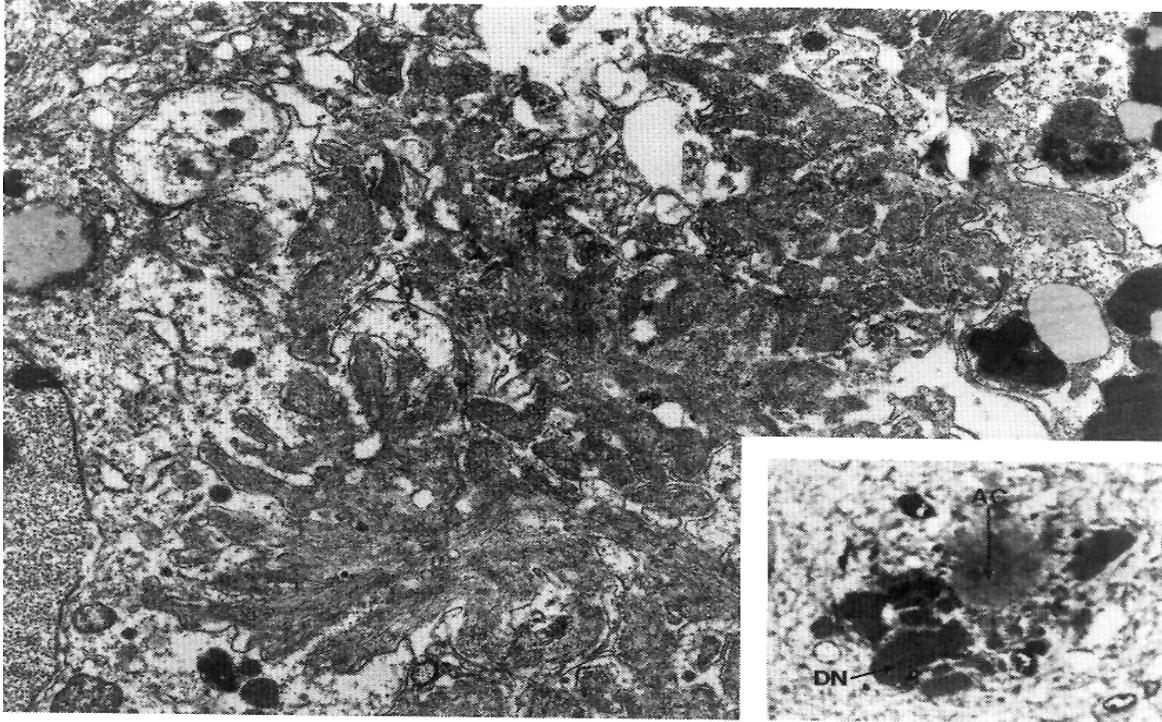
Diffuse: mostly unformed if protein without abnormal neurites
Neuritic: filamentous amyloid and dystrophic neurites
Dystrophy without PHF in normal aging
Dystrophy with PHF in AD
Primitive--without dense core of if protein
Mature--with dense core
Burned out::dense amyloid with reactive astrocytes, without neurites
(PHF, paired helical filaments.)



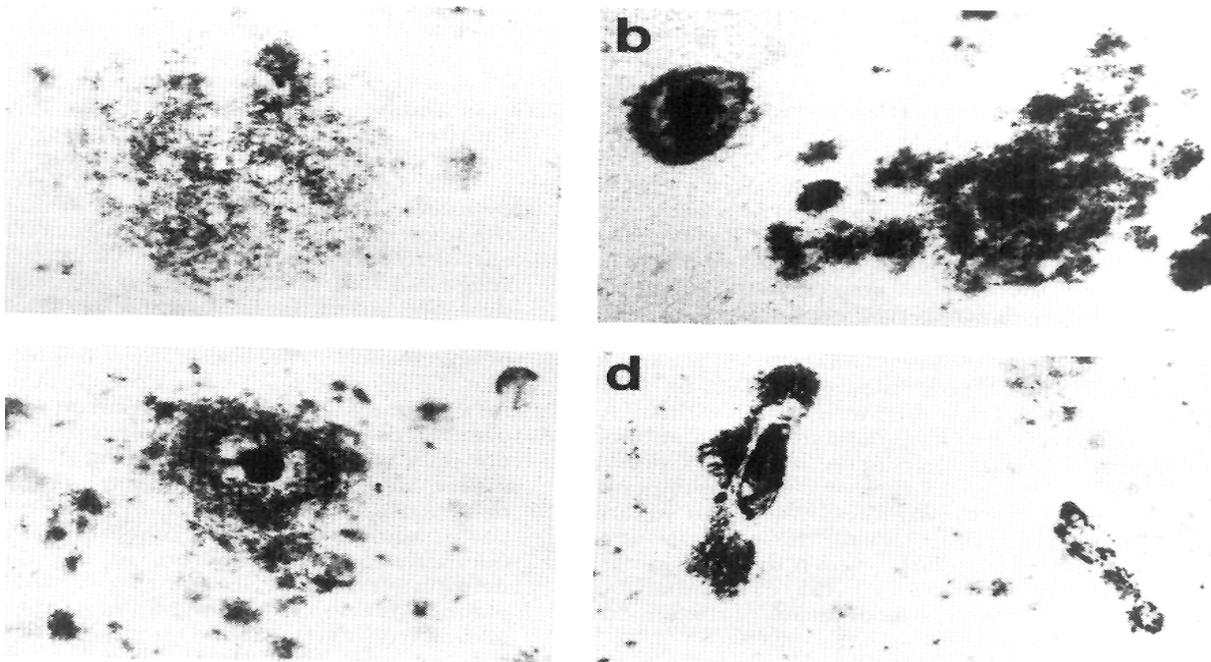
**FIG. 3.** Histochemical appearance of plaques in AD with silver stains, (a) Diffuse plaques stained with the Bielschowsky method. (b) Immature and mature plaques stained with the Bielschowsky method, (c) Neuritic component of a mature plaque stained with the Bielschowsky method. (d) Neuritic plaque stained with the Gallyas method.



**FIG. 4.** Thioflavin-S staining in Alzheimer disease. (a) Mature plaque with dense amyloid core (ac) surrounded by several tangles. (b) Neurofibrillary tangles in the entorhinal cortex layer 2. (c,d) Amyloid angiopathy (*arrow*).

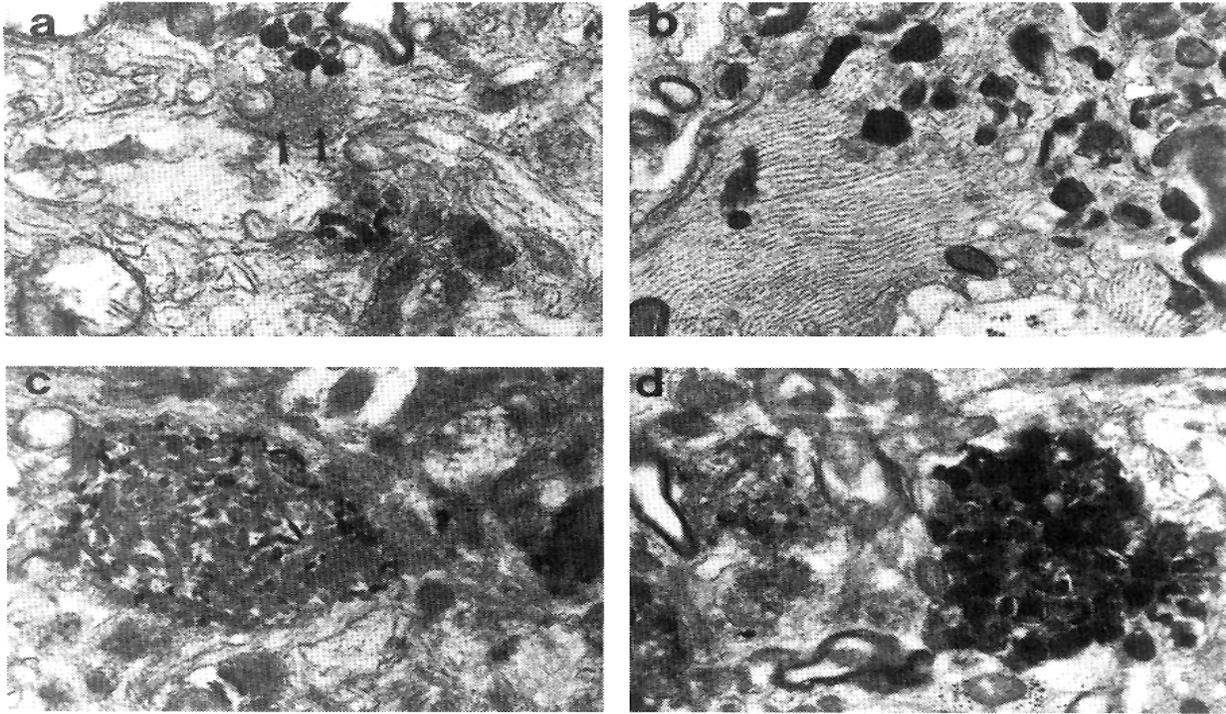


**FIG. 5.** Ultrastructural appearance of the amyloid fibrils in a mature plaque. Notice that the densely packed amyloid fibrils are surrounded by the membranes of a microglial cell. Inset: The light microscopic appearance of a semi-thin section of a mature plaque (toluidine blue) with a dense amyloid core (AC) and dystrophic neurites (DN).

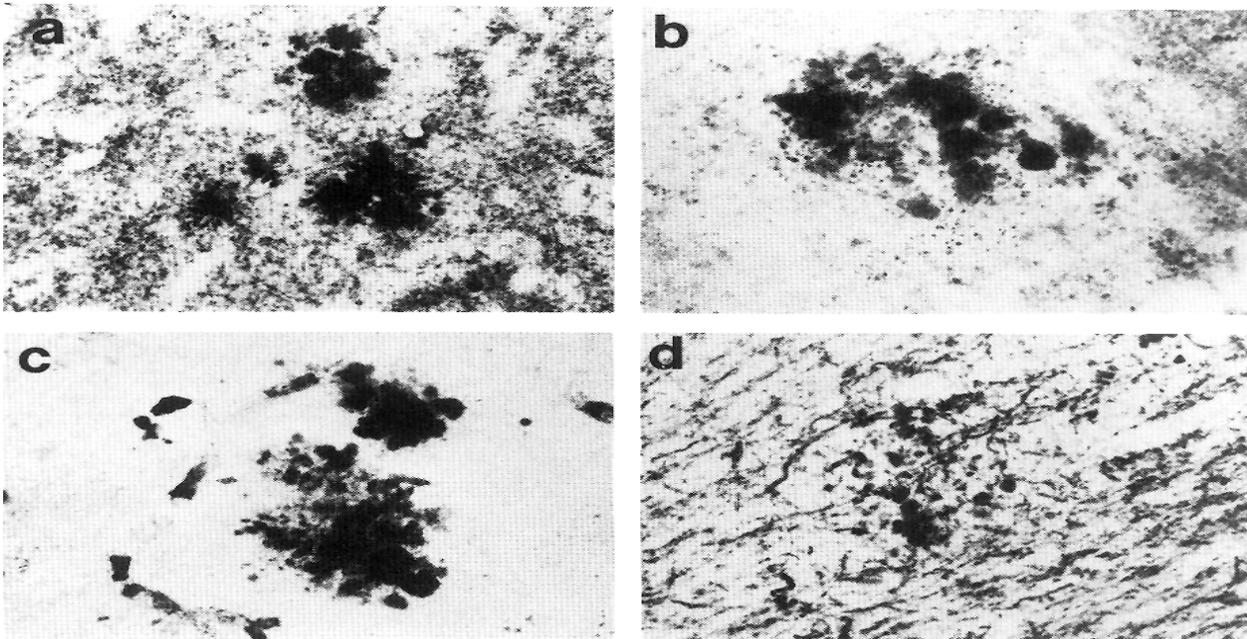


**FIG. 6.**  $\beta$ -Amyloid immunoreactivity in neocortex in AD. (a) Diffuse plaque. (b) Mature and immature plaque. (c) Mature plaque with dense amyloid core. (d) Amyloid infiltration in large parenchymal vessels.

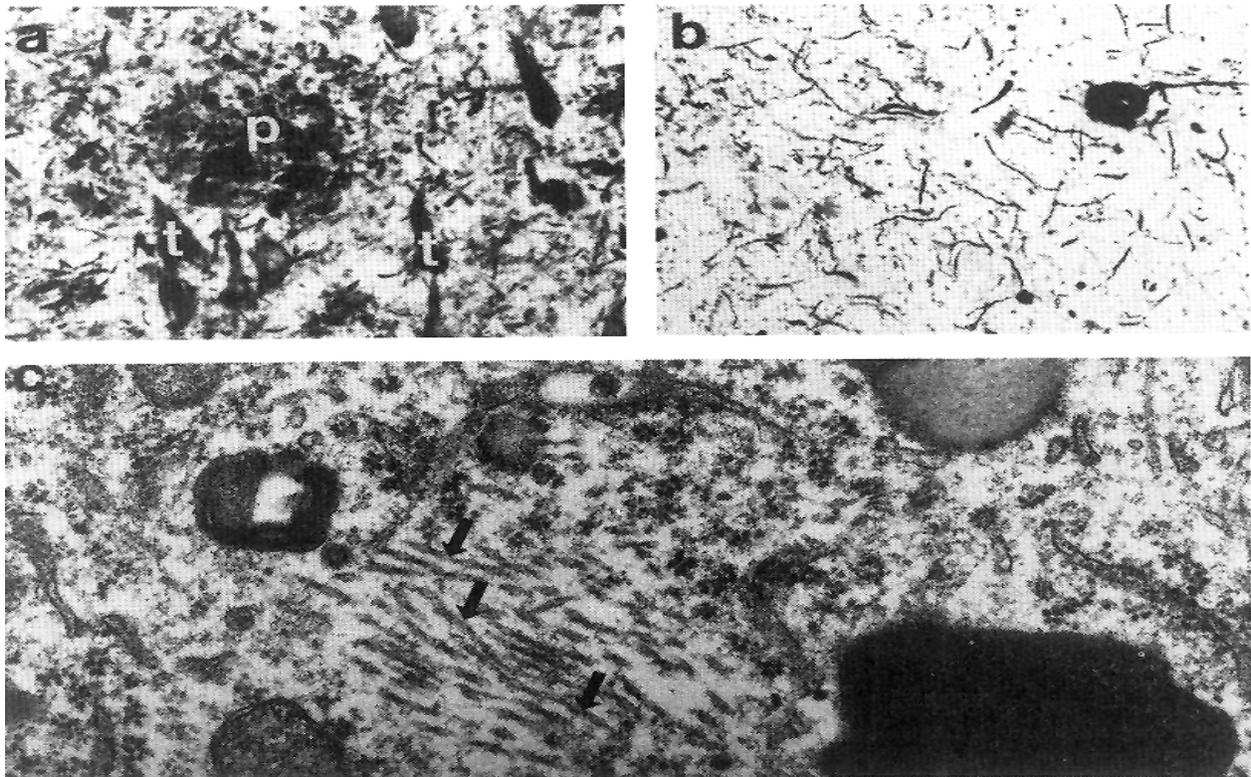
## Structural Basis of Cognitive Alterations



**FIG. 7.** Ultrastructural appearance of the neuritic component of mature plaque. (a) Mildly affected presynaptic terminals containing synaptic vesicles (*arrows*) and dense bodies. (b,c) Enlarged dystrophic neurites containing dense bodies resembling lysosomes and PHF. (d) Dystrophic neurites with abundant dense bodies.



**FIG. 8.** Immunocytochemical reactivity of the neuritic plaques. (a) The neuritic elements in the plaque are immunoreactive with an antibody against synaptophysin. (b) Immunoreactivity with an antibody against p65 (synaptic vesicle protein). (c) Neuritic plaques immunoreactive with an antibody against APP. (d) Neurites in the plaque reacted with an antibody against phosphorylated heavy neurofilament (SMI312).



**FIG. 9.** Structural composition of neurofibrillary alterations. (a) Neuritic plaque (p) and neurofibrillary tangles (t) are immunoreactive with an antibody against tau. (b) Tau immunoreactive neuropil threads. (c) PHF such as the ones indicated with the *arrows* are found in tangles and neuropil threads.

A second theory would have it that plaques develop from amyloid in the blood vessel wall arising from the systemic circulation (45). While some plaques are indeed associated with an amyloidotic vessel, the great majority are not (46). A third hypothesis came from study of human brain biopsies and of aged primate brain, which have shown clusters of dystrophic neurites in the virtual absence of amyloid (47). Some investigators have suggested that these damaged neurites release amyloid from their contained amyloid precursor. The amyloid forms fibrils and with the neurites develop into mature plaques. A fourth hypothesis has it that degeneration of the cholinergic neurons of the basal nucleus of

Meynert (NBM) gives rise to distant dystrophic terminals, which lead to the plaque formation (48). However, the reticular nucleus of the thalamus, which is heavily invested by

cholinergic neurites from the NBM, does not display plaques (49,50). Furthermore plaques contain neurites of several transmitter types (34). Most recently it has been suggested that a neurofibrillary tangle extruded from a dead neuron is the nidus of the plaque (51). However, plaques are found where there are no tangles, and extracellular tangles are found where there are few or no plaques. The two most popular of these hypotheses are those based on the diffuse plaque or on an origin from small clusters of dystrophic neurites.

### Tangles

While there can be little doubt that tangles are critical lesions in AD, they are by no means specific to the disorder. They are well known in the substantia nigra in postencephalitic Parkinson's disease (52) and in the neocortex in

dementia pugilistica (53). They have also been reported in the area of arteriovenous malformations and in hydrocephalus associated with mental retardation (54) as well as in subacute sclerosing panencephalitis (55). In normal aging there are often a few tangles in layer two of the entorhinal cortex and in the pyramidal cells of the CA I sector of the hippocampus. They are, however, very rare in the neocortex of the normal elderly.

Most cases of AD, on the other hand, display great numbers of tangles in the entorhinal and hippocampal areas and significant numbers in the neocortex as well as in the locus coeruleus and dorsal raphe. Among older patients (over 70 years of age) with the disease, about 10% to 15% with an otherwise clinically, structurally, and chemically identical disorder seem to have very few or no tangles in the neocortex (56). Some histopathologists prefer not to call these examples of AD, but to the current authors they seem identical except that the dystrophic neurites in the plaques in these cases may not contain PHF. Alzheimer's own files are said to contain numerous examples of this type (Harry Zimmerman, personal communication). An additional group of "plaque only" cases have constituted the Lewy body variant of AD (see chapter by Hansen). The tangle involves the cytoplasm of the larger neurons and only rarely affects small or medium ones. The lesion is made up of masses of intracellular argentophilic fibers (Fig. 10a,b), which stain brilliantly with thioflavin (with an appropriate excitation filter at about 440 nm) (Fig. 4b). Some of these bundles are flame-shaped and others are globoid. In the entorhinal cortex and the hippocampus, masses of these abnormal fibers can be found without the neuronal nucleus and other neuronal apparatus of

living neurons. These are the insoluble residue of tangles from neurons that have died. Such extraneuronal tangles are extremely rare in the neocortex. With the electron microscope the tangles are seen to be made of greater or lesser numbers of PHF first described by Kidd (57) as such and by Terry (58), who at the time believed they were twisted tubules (Fig. 9c). Further advances in microscopic resolution have brought

forth more detail as to the structure of these PHFs, such that there would seem to be at least four and possibly eight protofilaments (59). The latter appear to be arranged in the form of a tubule with an incomplete wall. The principal biochemical component of the PHF (Figs. 9c and 10c) is an abnormally phosphorylated tau protein (Figs. 2d and 10d) (60) (see chapter by Kosik and Greenberg). The tangles also react with an antibody discovered by Wolozin et al. (61) and named ALZ-50, the antigen of which is called A-

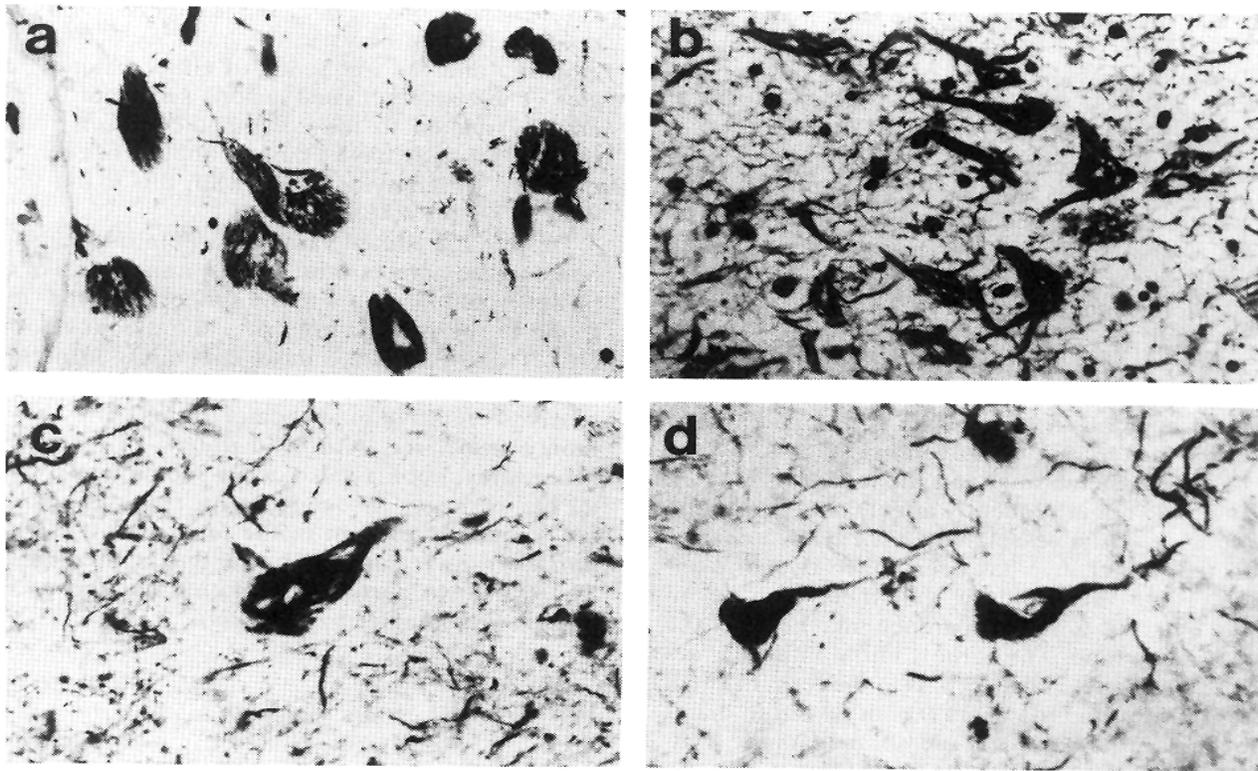
68 (see chapter by Davies). The ALZ-50 immunoreaction may well also show abnormal neurons prior to the formation of structural PHF.

The reaction is not only on the neurofibrillary tangles themselves, but also in cells without tangles, in areas in which neurons may be susceptible, including area CA3 in hippocampus (23). Recent studies have shown that tangles also immunoreact with antibodies against casein kinase II (62), protease nexin I (63), fibroblast growth factor (64), microtubule associated protein 5 (MAP 5) (65), and ubiquitin (24) and  $\beta$ -amyloid (66).

Given the apparent insolubility of the tangle made of PHF, the finding of extraneuronal tangles might well imply that the tangles are particularly toxic to neurons and are the principal cause of neuronal death in AD. Hippocampal and entorhinal neurons might well fall into this group, but cell death in the neocortex occurs in significant degree even in the absence of neurofibrillary tangles. The cell loss in tangle-free Alzheimer neocortex is as severe as in cases with tangles. Factors other than the tangle must be the major cause of neuron death in areas other than the limbic system.

### Neuropil Threads

Threads are relatively short, often curly, argentophilic and thioflavin positive fibers in the neuropil in the Alzheimer neocortex. In the presence of tangles their number increases significantly and in parallel with the clinical severity of the disorder (67). Most are dendrites, but others are axonal, some with a fine myelin sheath. Electron microscopically they are seen to



**FIG. 10.** Staining patterns of neurofibrillary tangles. (a) Tangles stained with Gallyas technique. (b) Stained with the Bielschowsky method. (c) Immunostained with antibody against PHF. (d) Immunostained with an antibody against tau.

contain PHF, while immunocytochemically they are characterized by anti-tau (Fig. 9b) and anti-ubiquitin reactivity (68). They may also contain a protein that is largely homologous with pancreatic thread protein and is called, in this instance, neuropil thread protein (69). The name is misleading in this context in that the protein is more related to pancreatic thread protein than to the structural neuropil threads of AD. At the present time a controversy still exists as to the significance and origin of the neuropil threads and dystrophic neurites in AD; while some groups postulate that they represent degenerating processes (70), others suggest that at least a subpopulation of them represent aberrant sprouting (25) neurites, based on the presence of the growth-associated proteins and the formation of synapses on the threads (71).

### Amyloid Angiopathy

Scholz (72) was the first to recognize amyloid in the vessels in Alzheimer disease. His report

followed that of Divry (73), who was the first to show that the homogeneous material in the plaque was made up of amyloid. Glenner and Wong (74) extracted leptomenigeal vascular amyloid in cases of AD and demonstrated its amino acid sequence. Infiltration of small blood vessel walls by  $\beta$ -amyloid (Fig. 6d) is present in all but a very few cases of AD. Small to medium-sized lepto-meningeal vessels and those of the cortex are the usual locations. The frequency is most intense in the occipital region, while the hippocampal area is quite often relatively spared. Cerebellar vessels, especially in the leptomeninges, are very commonly involved with this infiltrate. About one-third of normal elderly cases display mild to moderate amyloid angiopathy of the leptomeninges and usually less in the parenchyma.

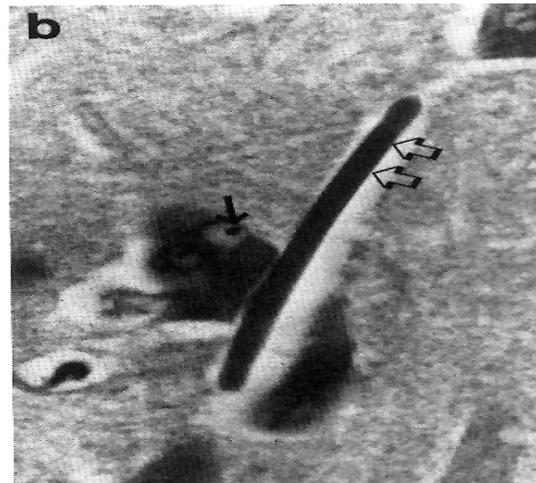
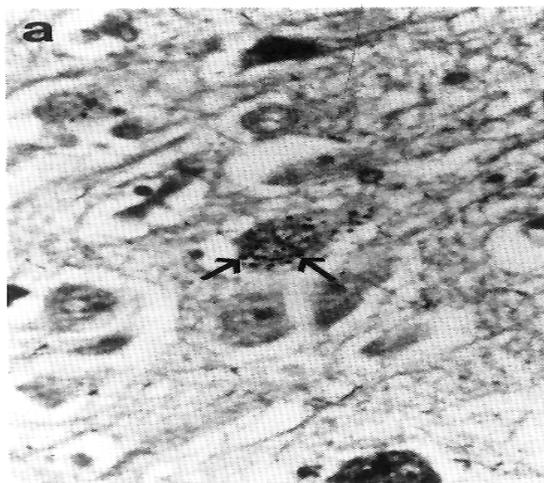
Amyloid appears as congophilic or thioflavin-positive fibrillar material in the adventitia (Fig. 4c,d), the outer basement membrane, and the media. It is often segmental, and not

infrequently affects only part of the circumference of the vessel. When cortical capillaries are affected, the change has been called dyschoric angiopathy. From the capillary wall there may be an infiltrate into the adjacent parenchyma beyond the basement membrane. The earliest mural infiltrate, according to Yamaguchi et al. (75), is in the form of small numbers of very fine filaments (about 80 nm in diameter.) located in the basement membrane. As the infiltration evolves, the fibrils thicken to about 10 nm and come to involve the media.

Given the greatest frequency in the occipital and cerebellar regions, it is clear that there is only a very poor correlation between the intensity of amyloid angiopathy and the frequency of either plaques or tangles. These parenchymal lesions seem not to be necessarily related to the congophilic vessels; although many plaques do

have a closely applied or even central capillary with amyloid in its wall, this is not the case with all plaques (46).

Despite the altered vascular wall in these instances, hemorrhages are rare in AD. In normotensive aging, however, hemorrhages in the subcortical areas may be found in the presence of cortical amyloid angiopathy (76). These bleeds are most commonly in parietal or occipital white matter in locations unusual for hypertensive cerebrovascular hemorrhages. They are commonly associated with head trauma or neurosurgical procedures, but may also occur spontaneously. Familial hemorrhages associated with amyloid angiopathy are frequently present in the familial amyloidosis reported from Iceland (77) and the Netherlands (78). These involve particular mutations of the precursor protein (see chapter by Robakis).



**FIG. 11.** Other neuronal alterations in AD. (a) Granulovacuolar degeneration (*arrows*) in pyramidal neurons of the hippocampus. (b) Pyramidal neuron in the hippocampal region displays a large Hirano body (*open arrows*) and granulovacuolar degeneration (*closed arrow*).

### Hirano Bodies

These structures, by far the most common in the hippocampal pyramidal layer, were first described by Hirano in specimens of the Guam-Parkinson-dementia complex (79). They appear

as eosinophilic rod-like structures either within or often adjacent to pyramidal neurons and are about 7 to 10  $\mu\text{m}$  in thickness (Fig. 11b). Electron microscopy revealed them to be made of alternating rows of filaments in longitudinal or cross section (80). Goldman (81) reported that

they react immunocytochemically with anti-actin. Galloway et al. (82) subsequently found that other muscle associated proteins such as tropomyosin are also present within these structures.

The Hirano bodies are by no means specific to AD, being found in normal elderly specimens as well as in other degenerative disorders. While the neurofibrillary tangle involves intermediate neurofilament and micro-tubule proteins, Hirano bodies appear to involve the proteinaceous components of microfilaments.

### Granulovacuolar Degeneration

Simchowicz (83) was the first to describe this lesion in 1911. It is readily recognized in hematoxylin and eosin (H&E) sections or in silver stains especially of the hippocampus, where vacuoles are present in the cytoplasm of the pyramidal cells. Each vacuole, usually measuring 3 or 4  $\mu\text{m}$  in diameter, contains a dense hematoxylinophilic, argentophilic granule, 1 or 2  $\mu\text{m}$  in diameter (Fig. 11a). The cells with these granulovacuolar bodies are relatively sparse in normal aging, but increase markedly in AD (84) and in several other disorders. Electron microscopy reveals a single membrane surrounding the vacuole, and a dense finely granular mass making up the granule. The latter displays immunochemical reactions to antitubulin (85), to ALZ-50 (86), and to certain antineurofilament antibodies (87).

### NEURONAL LOSS

Diminished concentration of larger neurons is readily apparent in the AD neocortex even with superficial examination using oversight stains such as H&E or cresyl violet. The loss has been quantified by several groups (88,89) by means of image analysis apparatus. Younger patients display considerably greater relative loss than do the older ones, but the loss is statistically significant in both groups. Our own studies in more than 70 patients with "pure" Alzheimer disease, aged 70 to 90, reveal a neocortical decrease of about 30% of neurons with cross section area greater than 90  $\mu\text{m}^2$  relative to

normal age-matched controls, while more than 20 younger patients between ages 50 and 69 sustained losses approaching 60% (90). These counts concerned the midfrontal cortex

approximately in area 46, the rostral superior temporal cortex of area 38, and the inferior parietal region in area 39. Again, the two age groups were compared with groups of age-matched normals. Ball (91) has shown severe loss of hippocampal pyramids in step serial sections. Hyman et al. (92) enumerated the great losses from the entorhinal area especially in its layer 2, thus isolating the hippocampus. Whitehouse et al. (93) were first to report the loss of neurons in the cholinergic basal nucleus of Meynert (also see ref. 94). This affects cholinergic activity in the hippocampus and cortex. The locus coeruleus also sustains major decreases in pigmented neurons affecting widespread noradrenergic activity (95). The dorsal raphe is similarly affected by neuronal loss and shrinkage (96). Despite these highly significant losses, the neuronal numbers do not correlate significantly with the severity of the disease as measured by global psychological tests of dementia.

The mechanism of cell death in AD is largely unknown. Among the hippocampal pyramids and the neurons of the entorhinal region, cell death seems closely related to the presence of neurofibrillary tangles, many of which are left behind in the neuropil when the neuronal nucleus and cytoplasm disappear. As to the neocortex, however, this does not seem to be true, since there is no apparent relationship between the presence of tangles and the number of neurons that have disappeared. There are many older patients with AD in whose cortex tangles are either entirely missing or very sparse. These cases display a neuronal decrement as severe as those with neocortical tangles (56).

Along with the loss of neurons there is an increased number of fibrous astrocytes as recognized in sections reacted with anti-glial fibrillary acidic protein (GFAP). In layers 2 through 6 of the neocortex the glial increase is about fourfold (97). The increased numbers of astrocytes are scattered throughout the

neocortex, but especially in association with plaques. This appears to be a reactive change rather than a primary one.

### SYNAPTIC ALTERATIONS

The major intellectual functions are largely dependent on the patterns of interconnectivity and plastic activity in the neocortex. The integrity of these microcircuits depends on the structural stability of the synaptic apparatus. During synaptogenesis postsynaptic specialization occurs before formation of the presynaptic site, but the development of the presynaptic element influences postsynaptic maturation. These complex cascades of events are regulated genetically in the neuronal soma by the transcription of specific synapse-associated proteins that become specifically compartmentalized in the specialized subcellular structures of the synapses.

Recent studies have shown that in addition to the traditionally described lesions (plaques and tangles) found in the AD brain, this neurodegenerative disease is characterized by neuronal loss, disruption of the neuritic cytoskeleton (76,98), altered corticocortical connectivity (99,100), and extensive synapse loss (29,101-107).

The development of antibody panels against synaptic proteins has made it possible to explore certain molecular alterations of the synapses in AD (30). Immunochemical and immunohistochemical work on the AD neocortex with the presynaptic marker synaptophysin (108,109) and with brain spectrin (25), has shown an average 45% decrease in presynaptic terminal density (29,103) (Fig. 12). Quantitative electron microscopic studies in AD biopsy and autopsy tissue from the prefrontal cortex have shown a 27% to 42% synapse loss, accompanied by extensive pathological changes in the synapses (101,105). As synapses are lost, remaining synapses develop an increased area of apposition between the pre- and post-synaptic elements. Synaptophysin immunoreactivity is also altered in certain regions of the hippocampus. Moreover, recent work with the synaptic marker EP10 has shown an age-related (normal) reduction in

the EP10 antigen in the caudate, but not in the hippocampus or temporal and occipital cortex. In AD, there was a significant reduction in EP10 immunoreactivity in the hippocampus and neocortex, again suggesting a selective, regional synaptic loss (104). While synaptic density is generally diminished in AD cortical neuropil as compared to age-matched controls, the reduction is no greater within the diffuse plaques than in the neuropil outside them (110) (Fig. 2a). Synapse loss was greatly accentuated, however, within immature and mature plaques (109, 110), and abnormal synapses are clustered around dendritic neuropil threads (71). These findings suggest that the pathogenic process in AD might commence with synapse loss and neurodegeneration rather than with a primary deposition of amyloid  $\beta$ -protein.

Work on aged monkeys as well as on AD cortex has shown that the abnormal neuritic elements in the plaque contain several synaptic and axonal specific proteins (30,111). These studies support the possibility that plaque formation might start with synaptic and neuritic alterations accompanied by accumulation of amyloid precursor protein (APP) in the altered neurites, followed by amyloid deposition. APP, a molecule often suggested as centrally involved in AD, has been shown to be rapidly transported in the axon to the presynaptic site (112). Immunoelectron microscopic studies as well as confocal laser imaging have localized APP in the presynaptic terminal (113). 3-dimensional reconstruction of the plaques showed that anti-APP was colocalized with anti-GAP43 in almost 60% of the aberrant sprouting neurites (20). Other studies have shown that APP and its proteolytic fragments are present in growing neurites in the fetal brain (114), and in vitro experiments have suggested that, depending on its concentration, APP and its fragments could be neurotoxic (115) or neurotrophic (116). Taken together these studies suggest that altered synaptic function might be associated with the abnormal processing of APP.

The mechanisms by which synapses are damaged and lost are poorly understood. Some possible explanations are (a) receptor-mediated neurotoxic effect of endogenously produced

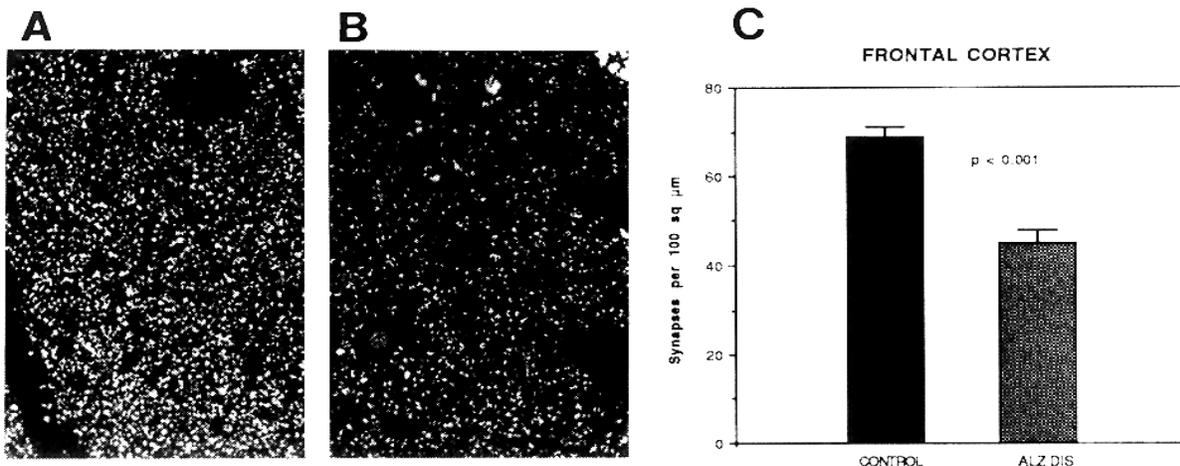
substances or an exogenous neurotoxin, (b) failure of neuronal plastic modulatory mechanisms to maintain synaptic integrity due to altered expression or processing of molecules involved in neuronal signaling and survival, and abnormal axonal transport (117). Accumulation of APP in the presynaptic terminal might interfere with neurotransmission and synaptic plasticity. At the present time there are no *in vivo* models to test these hypotheses.

### ALZHEIMER LESIONS IN THE NONDEMENTED ELDERLY

The neuropathologic diagnosis of Alzheimer disease is straightforward when presenile patients with AD are compared to age-matched controls. The resulting differences are striking, since the AD patients will have myriads of

plaques and tangles while the controls will have none. Such a clear-cut distinction between disease and normalcy can become blurred when considering AD in the elderly. A few Alzheimer lesions can be found in many nondemented subjects of advanced age. This raises a nosologic, if not philosophical, question. Specifically, does the presence of some AD pathology, qualitatively indistinguishable from that seen in florid AD, constitute incipient (preclinical) AD, or merely normal aging.<sup>9</sup>

Neurofibrillary tangles (NFT) in the brains of the nondemented elderly show the same cytoarchitectural predilection as do NFT in tissue from AD patients. If they occur at all, these NFT will be found in small numbers in the medial temporal lobe, specifically the entorhinal cortex (layers 2, 3, and 4) the CA1/subicular zone



**FIG. 12.** Synaptic loss in Alzheimer's disease. (A) Neuropil from the frontal cortex of a normal nondemented aged individual displays abundant presynaptic boutons immunolabeled with an antibody against synaptophysin and imaged with the laser scanning confocal microscope. (B,C) In AD there is a significant reduction of synaptophysin immunostained presynaptic boutons.

(especially the prosubiculum), and the amygdala.

Many of the nondemented elderly are entirely free of senile plaques. However, if diffuse deposits of  $\beta$ -amyloid are construed as a type of plaque, then about half of all older controls have at least a few such lesions (118,120,121). Old normals with neocortical diffuse plaques are

more likely than old controls without them also to have small numbers of NFTs in the cytoarchitectural areas of tangle predilection in the roedial temporal lobe (92,122). This simultaneous appearance of neocortical diffuse plaques and roedial temporal lobe NFTs seems to imply an early developmental stage of AD, in which the lesions are not yet sufficiently

burdensome to produce symptoms. However, according to some authorities (98), once elderly normal controls add dystrophic neurites to their diffuse plaques, either in the form of neuritic plaques or neuropil threads, dementia appears. Nevertheless, at least small numbers of unequivocally neuritic plaques can be encountered in some cognitively intact old people, and great numbers in a few.

### **DIAGNOSTIC CRITERIA: SENSITIVITY AND SPECIFICITY**

Traditionally, the final neuropathologic diagnosis of AD has resulted from a clinicopathologic correlation, as in Alzheimer's (8) original case. That is, when a brain from a clinically demented patient has many senile plaques and neurofibrillary tangles, it is diagnosed as showing "Alzheimer disease." As discussed above, however, the appearance of AD pathology is not an "all or none" phenomenon, and the question often arises as to how much AD pathology is enough to warrant the diagnosis. This issue is particularly germane when the neuropathologist examines a brain without knowing the patient's cognitive status. To address this problem, various diagnostic criteria have been proposed that delineate cutoff levels of AD pathology, above which diagnoses are made and below which they are not. Such criteria are arbitrary and, to a degree, inconsistent with our current understanding about the evolution of AD pathology. Nevertheless, for practical purposes, we must make such diagnostic decisions since the neuropathologic staging (118) of AD pathology in lieu of the current "AD or not AD" nomenclature is not widely practiced.

The most often cited diagnostic criteria for AD are those from a conference held at the National Institute on Aging (NIA) (123). These are the most sensitive of the commonly utilized criteria, and are based on age-adjusted neocortical counts of senile plaques. Specifically, they state that minimal neocortical plaque densities per square millimeter requisite for the diagnosis of AD are 8 or more for patients 50 to 65 years; 10 or more for patients 66 to 75 years,

and 15 or more for patients older than 75 years. The NIA criteria do not specify plaque type or neocortical region. While these criteria have proven very useful, they are widely criticized as being too sensitive and insufficiently specific since some nondemented elderly have enough plaques to warrant an AD diagnosis. More recently, the multi-institutional Consortium to Establish a Registry for Alzheimer's Disease (CERAD) has published diagnostic criteria for AD based on a semiquantitative assessment of specifically *neuritic* plaque frequency, correlated with the age of the patient to arrive at an "age-related plaque score" (124). Neocortical tangles are not requisite for a CERAD diagnosis of AD, and the pathologic changes in the hippocampus, entorhinal cortex, and amygdala are not considered in arriving at a diagnosis. However, the presence or absence of a clinical history of dementia is figured into the CERAD criteria. Even more stringent diagnostic guidelines that demand neocortical neurofibrillary tangles before a diagnosis of AD can be rendered may be too specific and insufficiently sensitive, since significant numbers of demented AD patients lack neocortical tangles (56,118). These problems of diagnostic sensitivity versus specificity are precisely those one would anticipate when attempting to draw a line somewhere along a spectrum. This spectrum stretches all the way from the rare neocortical diffuse plaques and scanty medial temporal lobe tangles seen in some nondemented elderly brains to the shriveled walnut brains of severe AD patients ubiquitously laden with myriads of plaques and tangles. We use the term "Alzheimer's changes" to describe brains from nondemented elderly patients whose neocortical plaque density is insufficient to warrant the diagnosis of AD according to NIA and CERAD criteria. We also diagnose AD if plaques and tangles are numerous, even without a dementia history. Our reasoning in so doing is that all AD patients must pass through a preclinical or incipient phase, and the absence of symptoms is not synonymous with an absence of disease.

## THE CAUSES OF DEMENTIA IN ALZHEIMER DISEASE

It is increasingly clear that Alzheimer disease is genetically heterogeneous (see chapter by Hyslop) even while the phenotype is relatively homogeneous at least at the tissue level. It is equally clear that each of the many pathological cerebral alterations described in this chapter can contribute in varying degree directly or indirectly to the dementia. The most common belief seems to be that there must be a single causal cascade in AD, in which a primary lesion induces a second effect, then a third, and a fourth, ultimately leading to the clinical symptoms. This need not be true. One branch of the pathologic cascade might lead to an asymptomatic alteration, another branch to a significant mechanism for dementia, and a third branch to changes that contribute in only a minor fashion.

To be more specific, the most commonly held hypothesis contends that amyloid is the central factor in AD and a direct cause of dementia (125,126), either because amyloid has a toxic effect (115), or because its mass physically compresses cerebral tissue. In our extensive studies of many well worked up cases of pure AD there is not a significant statistical correlation between the number of plaques per unit area in the cortex and the severity of the dementia (13). Furthermore, there have been several autopsy reports of cognitively normal elderly with huge numbers of cerebral plaques and a very large amyloid load. It has been shown *in vitro* that the A $\beta$  protein under certain circumstances, especially when it has been formed into filaments, does have toxic and inhibitory effects on neurite outgrowth (127). Others have shown that soluble amyloid seems to cluster about the perikaryon in neuron cultures (128). However, when amyloid is injected into the brain in *in vivo* experiments it seems not to demonstrate any particular toxic effect upon neurons or their processes (129). If a toxic factor is diffusing out of the plaque core, then one would expect a gradient of damage, most severe adjacent to the plaque and lessening as one proceeds outward into the neuropil. Such a gradient has not been

seen.

It has also been suggested that the amyloid load simply squeezes the brain tissue as it does in the amyloidotic liver or kidney (Wisniewski, personal comment). When secondary amyloidosis infiltrates the liver, it causes enlargement of that organ such that its capsule is tense. The kidney responds very similarly to the extensive glomerular infiltrate of amyloid. In neither case does the organ shrink as does the brain in AD. The AD brain is not known to swell at any stage of the disease.

Another possible detrimental effect of amyloid is that it may tie up or block sites on the amyloid precursor molecule that mediate trophic activity (130,131). But again, the facts that the amyloid load is not proportional to the dementia and that a gradient of damage is not found in the neuropil argue against this role as having a major effect.

Dementia characteristic of the Alzheimer type is commonly found in cases where cortical tangles are either rare or essentially absent. Thus cortical tangles do not correlate strongly with the severity of the dementia as measured by global tests (13). However, we have recently found that tangles in the basal nucleus of Meynert do correlate strongly with loss of memory in global analyses such as the Blessed test, which is largely concerned with memory, and with the memory component of the Dementia Rating Scale (132).

The average concentration of tangles, plaques, Hirano bodies, granulovacuolar bodies, neuron loss, and synaptic loss are clearly and significantly different in AD from those found in the normal age-matched population. However, very few of these lesions correlate in the form of a linear regression with the severity of clinical disease. Tangles in the substantia innominata, as indicated above, correlate with the degree of memory loss, while to date prefrontal synaptic loss is by far the strongest correlate with other high cognitive functions. The synapse loss in midfrontal cortex as measured either by electron microscopy (133) or by immunocytochemical (13) or immunochemical means has shown very powerful correlations with the Mini-Mental State Examination (MMSE) and with the

nonmemory components of the Dementia Rating Scale of Mattis.

Stepwise regression of the Blessed Information Memory Concentration Test (which deals predominately with memory) showed that 53% of the variance ( $R^2$ ) is related to basal nucleus tangles, with 26% related to midfrontal synapse density and 7% to remaining large neurons in the basal nucleus; 14% of the variance is not accounted for. The same sort of analysis on the MMSE, which deals predominately with cognitive abilities other than memory, showed that 50% of the variance was related to midfrontal synapse density, 24% to basal nucleus tangles, 13% to basal nucleus large neurons, 6% to basal nucleus synapses, 5% to frontal plaques, and 2% unaccounted for (132).

An important issue now is to account for the mid-frontal synapse loss. Those parameters that correlated most strongly were large neurons, hyperphosphorylated tau reactive neurons and tangles all in the inferior parietal area and tau-PO4 reactive neurons in the superior temporal region. Neither frontal parameters nor plaques were significant (Terry and Masliah, unpublished data).

It is thus apparent that the lost frontal synapses are terminals from distant neurons rather than local ones, and that those projection neurons are either missing entirely or have cytoskeletal abnormalities. If one accepts the concept that synapse loss is the immediate cause of dementia, then the cause of synapse loss is primarily neuronal injury with only a minor contribution from the deposition of visible amyloid.

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# **Part 4**

# **Epidemiology**



# The Epidemiology of Dementia and Alzheimer Disease

Robert Katzman and Claudia Kawas

**Case Identification: Criteria for the Diagnosis of Dementia and Alzheimer Disease Used in Epidemiological Studies**

**An Overview of Advances and Questions that Arise Case-Control Studies of AD**

The EURODEM Analyses

**Prevalence of Dementia and AD in Community Studies**

Case Ascertainment and Diagnostic Criteria for Dementia and AD in Community Studies

Age-Specific Prevalence Rates

Education, Occupation, and the Prevalence of Dementia

Gender and Risk of Dementia

Other Demographic Factors and the Prevalence of Dementia

The Relative Prevalence of AD and Vascular Dementia

**The Incidence of Dementia**

Longitudinal Studies of Dementia

**Mortality**

**Risk Factors for AD and Causality**

**Biological Plausibility**

**Epidemiology of AD: A Public Health Perspective**

**AD as a Chronic Disease**

**References**

Our understanding of the epidemiology of Alzheimer disease (AD) has advanced rapidly during the past decade. Community (population) studies in many countries have confirmed that the prevalence of AD (and of vascular dementia) rises in an approximately exponential fashion at least between ages 65 and 85, doubling with every 5 years of age; comparison of population studies between different countries has shown age-specific prevalence rates to be similar *within a factor of two* among countries as diverse as China, Japan, Great Britain, France, Italy, and the United States. From these population studies other demographic factors, including gender (women may be more susceptible to AD than men), poor education, and perhaps certain occupations have emerged as important putative risk factors. Moreover, case-control and longitudinal studies have confirmed the importance of family history as a major risk

factor, and other, somewhat unexpected risk factors, such as head trauma and coronary artery disease, have been identified. From these findings, together with current knowledge of molecular, genetic, and pathological features of AD, a picture emerges of the interaction over time of these risk factors with the biological factors that lead to the development of the Alzheimer process.

## CASE IDENTIFICATION: CRITERIA FOR THE DIAGNOSIS OF DEMENTIA AND ALZHEIMER DISEASE USED IN EPIDEMIOLOGICAL STUDIES

These epidemiological advances have resulted largely from the development in the early 1980s of a consensus on acceptable diagnostic criteria for dementia and AD. The importance of a consensus in regard to "caseness" is basic to epidemiological studies. The most widely accepted diagnostic criteria for dementia are based on the principles introduced in 1980 in the third edition of the American Psychiatric Association's *Diagnostic and Statistical Manual*

R. Katzman: Department of Neurosciences, University of California-San Diego School of Medicine, La Jolla, California 92093-0949.

C. Kawas: Department of Neurology, Johns Hopkins Bayview Campus, Baltimore, Maryland 21224.

of *Mental Disorders* (DSM-III) (1) and the subsequent delineation of criteria for "probable" AD by a work group established jointly by the National Institutes of Neurological and Communicative Disorders and Stroke (NINCDS) and Alzheimer's Disease and Related Disorders Association (ADRDA) (2). Before adoption of the DSM-III criteria, the diagnosis of dementia had been subject to error rates as high as 30%, in part owing to confusion of the diagnosis of dementia and depression [see, for example, Ron et al. (3)]. With the use of DSM-III criteria, the accuracy of diagnosis of the dementia syndrome has increased to over 98% in clinical series (4). Consequently, in case-control studies in which cases of AD are selected from the clinic population, the likelihood of a clinical case being AD is very high.

The accuracy of current diagnostic criteria in the clinic does not necessarily apply to community or population studies. Here the sensitivity and specificity of diagnostic criteria are likely to be the focus of intensive investigation in the next several years. In community studies the difficulty of diagnosing dementia in elderly subjects who are very ill, in those with marked hearing or visual impairments, and in some with limited education decreases the accuracy of diagnosis. Moreover, it has become evident that the conservative DSM-III and NINCDS/ADRDA criteria may result in classification of mild dementia as being questionable or normal. For example, in the Shanghai survey to be discussed below, for every two cases that met DSM-III criteria for dementia there was one case classified as "possible dementia" that did not meet DSM-III criteria; subsequent follow-up has shown that many of these subjects were indeed in the early stages of dementia and in this sense had been misclassified.

## **AN OVERVIEW OF ADVANCES AND QUESTIONS THAT ARISE**

Despite these problems, which must be addressed during the next decade, a number of clear-cut findings have emerged, and are summarized as follows:

1. Age is the single most important risk factor for dementias of all kinds, including AD. The prevalence of dementia doubles approximately every 5 years in individuals between the ages of 65 and 85. Data on individuals below age 65 or above age 85 are insufficient to be certain whether this apparently exponential relationship holds; very likely a more complex relationship such as the logit model would be necessary to account for a broader age range. This is important as individuals over the age of 85 represent the fastest growing segment of our population and the accurate projection of future cases will depend on the correct model.

2. In most, but not all, studies, women seem to be at greater risk for dementia, and in virtually all studies women are at greater risk for AD, whereas men appear to be at somewhat greater risk for vascular dementia. If AD is indeed more common in women, this might imply an effect of hormones on the development of AD, which could have important public health and therapeutic consequences. It is also possible that some of these differences could be accounted for by secular effects such as the relative lack of education (see 3, below). Moreover, more prevalent cerebrovascular disease may lead to overdiagnosis of vascular dementia in males and hence artifactually increase the proportion of women with the clinical diagnosis of AD.

3. Lack of education is a risk factor for dementia, probably for both Alzheimer and vascular dementia. An uneducated individual over 75 is at about twice the risk for dementia as is one who has completed at least eight grades of school.

4. A history of AD in a first-degree relative--mother, father, brother, or sister--increases the risk of developing dementia approximately fourfold. Although this is certainly true over a wide range of ages, it is not clear if it holds for those over age 80.

5. Head injury, either a single episode leading to unconsciousness or hospitalization, or repeated head injuries, as in the case of boxers, is a risk factor for AD with a relative risk (RR) greater than 2. Concern that this risk factor, which has been noted fairly consistently in case-

control studies, might be due to selective recall by family or friends of individuals with AD is counterbalanced by the observation that head injury often produces diffuse B-amyloid plaques in the brain, which are similar to those present in AD.

6. Intriguing preliminary data, which require verification, suggest that in the very elderly, myocardial ischemia may be a risk factor for dementia, particularly in women, again acting through the production of diffuse B-amyloid plaques.

7. Smoking has frequently been found to be a protective factor for AD in various case-control studies, but there are several uncertainties concerning this risk factor; for example, are smokers more likely to suffer strokes, so that those who develop AD are misdiagnosed as having multi-infarct dementia (MID)? If nicotine is a protective risk factor, then the capacity of this drug to up-regulate its receptors might be involved in its protective action.

8. An inconsistent but intriguing potential risk factor is maternal age. An increase in AD has been reported in some studies, but not in others, in subjects born to mothers over the age of 40 years.

9. A number of other risk factors have been reported in one or two case-control studies, but not confirmed by other studies. Some of these, such as exposure to aluminum, may act as very weak risk factors.

## CASE-CONTROL STUDIES OF AD

Epidemiologists recognize that case-control studies offer the most cost-efficient method of identifying risk factors. As cases and controls are usually matched in terms of age, gender, and socioeconomic characteristics, these particular demographic variables cannot be ascertained as risk factors within such studies. However, differences in coexistent diseases and in the history of various exposures can be identified. Normally, when such clues have been found, it is preferable to carry out prospective studies in which exact exposure to a risk factor can be determined more accurately to verify the findings. Regarding AD, a large number of case-

control studies have now been carried out that have led to identification of interesting putative risk factors. Such case-control studies have an advantage over population studies in that subjects who unequivocally meet the criteria for dementia and probable AD are normally included as cases. Hence, the cases meet the best available clinical description of AD.

A case-control study carried out approximately 10 years ago by Heyman et al. (5) should be noted because of its superb methodological design. The AD cases were recruited from known patients and were each required to have an informant who could give a history. Similarly, the controls who were included also had an informant available so that histories for AD patients and controls were gotten from informants for both the cases and the controls. The controls were sought by random-digit dialing of the last four digits of the telephone number of each case, thus obtaining someone in the neighborhood of the case, so that an age- and gender-matched individual in the same neighborhood as the case was chosen. Some degree of socioeconomic balance was assured on the basis of this random digit dialing. As anticipated, family history was a strong risk factor. A new and striking risk factor to come out of the study was the existence of a history of head injury up to 30 years prior to the onset of AD. The odds ratio approached 6 comparing the history of head injury in cases with that in controls. Head injury was defined as one sufficient to produce unconsciousness. Another possible risk factor found was that of prior history of thyroid disease.

Similar findings of head injury as a risk factor were obtained by Mortimer et al. (6) in a case-control study involving Alzheimer patients seen at a Veterans Administration (VA) hospital. In this study, some of the instances of head injury could be verified with prior army or VA hospital charts. Subsequently, a number of case-control studies supported the importance of head injury as a risk factor, while others found very little effect.

## The EURODEM Analyses

To deal with this variation in reports of risk factors, a European group (EURODEM) brought together the principal investigators of 11 case-control studies [including those of Heyman et al. (5) and Mortimer et al. (6)] and obtained their agreement to make their data available so that combined analyses could be carried out (7). All of the studies had used DSM-III or NINCDS/ADRDA criteria. The EURODEM group selected 11 case-control studies as meeting the standards for their collaborative reanalysis. These included studies from Australia [Broe et al. (8)--170 cases]; Finland [Soininen et al. (9)--63 cases]; Italy [Amaducci et al. (10)--116 cases]; Japan [Kondo et al. (11)--34 cases]; Netherlands [Hofman et al. (12)--198 cases]; and United States--Bedford, Massachusetts [Shalat et al. (13)--106 cases], Denver [Chandra et al. (14)--64 cases], Durham, North Carolina [Heyman et al. (5)--46 cases], Minneapolis [Mortimer et al. (6)--78 cases], Rochester, Minnesota [Kokmen et al. (15)--192 cases], Seattle [Graves et al. (16)--130 cases]. Most of the cases used in the EURODEM analysis were obtained from hospitals or clinics. In various analyses, specific

**TABLE 1.** EURODEM case-control studies: risk factors for AD

Variable	Cases	Controls	Odds ratio	95% CI
Family history of dementia	305/894	140/894	3.5	2.6-6.9
Family history of Parkinson disease	20/312	8/294	2.4	1.0-5.8
Head injury	87/1,059	50/1,059	1.8	1.3-2.7
Head injury in sporadic cases	31/304	14/304	2.3	1.2-4.8
Maternal age >40	47/446	28/447	1.7	1.0-2.9
Thyroid disease	110/994	115/991	1.0	0.8-1.3
Hypothyroidism	17/655	8/732	2.3	1.0-5.4
Down syndrome	20/588	7/615	2.7	1.2-5.7
Depression in late-onset (>70) cases	41/524	18/509	2.4	1.4-4.4
Ever smoked	477/899	563/955	0.78	0.62-0.98

CI, confidence interval.

series had to be excluded for analysis. For example, the Bedford series excluded individuals with history of severe head trauma and could not be used for study of head injury as a risk factor. Individuals from all studies met NINCDS/ADRDA or DSM-III criteria for probable dementia. Major findings from the EURODEM reanalysis are shown in Table 1.

### *Head Injury as a Risk Factor for AD*

In regard to head injury, the seven studies pooled (N = 1,059 cases, 1,059 controls) included both those that found a strong effect (5,6,10), and those that had reported no significant effect (14,15). When pooled, a highly significant effect of head injury was found with a risk ratio of approximately 1.82 and 95% confidence intervals (CI) of 1.26 to 2.67 (17). Stratified analysis showed stronger association in cases without a positive family history of dementia (RR = 2.31) than in familial cases (RR = 1.42) and was greater for males than females, but was the same for those with onset before age 70 and those with onset after age 70. There was no interaction effect between head trauma and family history, suggesting that these factors operate independently.

Thus, the data from case-control studies are consistent enough that head injury can now be regarded as a likely risk factor for AD. In a later section we will discuss a plausible biological mechanism linking head injury and AD. Epidemiologically, however, there is always the problem of selective recall in case-control studies. Could family members, "the informants," of the cases have remembered head injuries over a period of time when they were concerned about the patient's progressive dementia, whereas the relatives of the control, or the controls themselves, would not have thought about prior head trauma and not have recalled as many instances? Certainly, such selective recall could have occurred, but the fact that head injury was found to be such an important risk factor in the very first case-control studies at a time when it was not

thought to be a risk factor and the fact that other important life events that might have been selectively recalled were not consistently present among individuals with AD suggest that this is indeed a true risk factor.

### ***Family History as a Risk Factor for AD***

Next to age, the predominant risk factor for AD is that of family history, that is, the occurrence of AD in a first-degree relative (mother, father, brother, or sister). The EURODEM analysis reported by van Duijn et al. (18) utilized data from eight of the case-control studies. The overall relative risk was 3.5 (95% CI = 2.6-4.6). The relative risk was highest in those with onset at ages 60 to 69 (RR = 5.3; CI = 2.8-10), but still significant in those with onset between ages 70 and 79 (RR = 2.3; CI = 1.4-

3.6) and those with onset after age 80 (RR = 2.6; CI = 1.3-5.2). In individuals who had two or more first-degree relatives, the relative risk increased to 7.5 (3.3-8.7). Surprisingly, the relative risk of AD for those with a positive family history of Parkinson disease was 2.4 (1.0-5.8), an interesting but not quite significant finding. Similarly, the association between AD and family history of Down syndrome was just significant, the relative risk of 2.7 with a 95% confidence interval of 1.2-5.7.

### ***Does Down Syndrome Occur More Frequently in AD Families?***

It has long been known that individuals with Down syndrome develop the neuropathological features of AD by age 35 (19). The inverse relationship, that is, an increase in children with Down syndrome in families in which one member has AD, was first reported by Heston (20) in 1977 and is apparently confirmed by the EURODEM study as noted above (RR = 2.7, 95% CI = 1.2-5.7) (18) although others (21,22) have not been able to demonstrate such a relationship. The obvious possibility, however, that AD subjects might have a triplication of some chromosome 21 genes has not been supported by direct

analysis (23,24). Another risk factor that was sought because of the Down relationship was an effect of *advanced maternal age* reported by Cohen and Eisdorfer (25) in 1982. Almost immediately after publication of this finding, both positive and negative reports were published (5,6,22,26-29). In the EURODEM reanalysis (29) only four studies addressed this issue; these showed a relative risk of 1.7 for maternal age over 40 (29), but this was not statistically significant with a 95% confidence interval of 1.0-2.9. Hofman et al. (30) recommended further investigation of this question.

EURODEM reanalyzed a wide variety of putative risk factors that had been addressed by the constituent case-control studies. Detailed analysis of prior alcohol consumption in terms of average weekly intake failed to show any excess risk (31). In this regard, case-control studies in which NINCDS/ADRDA criteria are used are likely to fail to identify a relationship between alcoholism and AD since the diagnostic criteria for probable AD would exclude individuals with severe alcoholism who could have an alcoholic dementia. In a recent population-based case-control study from Stockholm (32) that used modified DSM-III criteria (33) for the diagnosis of AD, a strong effect of increased alcohol consumption (RR = 4.4; CI = 1.413.8) was found. The possibility of such a relationship needs to be investigated in prospective studies.

A disturbing finding reported both in case-control and in longitudinal studies is a possible protective effect of smoking in regard to AD. Thus in the EURO-DEM reanalysis, a statistically significant inverse relationship between smoking and AD "was observed at all levels of analysis, with a trend toward decreasing risk with increasing consumption ( $p = .0003$ )" (31, p. S48). Although this relationship might be due to an actual protective effect of nicotine (which may upregulate acetylcholine nicotinic receptors) or to an effect of smoking on survival, another effect of smoking might be to increase the risk of strokes in AD so that misdiagnosis as

vascular dementia would occur.

Thyroid disease and hypothyroidism as risk factors for AD were initially reported by Heyman et al. (5). A history of hypothyroidism was marginally significant as a risk factor in the EURODEM analysis (Table 1) (34). In regard to psychiatric history and stress, no relationship of AD to death of spouse, death of a child, or divorce was found (35). In some cases of AD, depression occurs as an early symptom, often preceding diagnosis. In the EURODEM analysis, however, depression occurring more than 10 years before AD onset, although infrequent, was a significant risk factor (RR = 2.0; CI = 1.06-3.80) (35).

In the popular press, exposure to aluminum or aluminum products has been the most feared risk factor for AD. The failure of subjects undergoing renal dialysis who ingested large amounts of aluminum ant-acids to develop AD would militate against the importance of ordinary aluminum exposure (36). Indeed none of the case-control studies has found a relationship of AD to aluminum antacid intake or use of aluminum cookware, although a single study reported a minimal increased risk with the use of aluminum anti-perspirants (37). For an expanded discussion of aluminum in AD, see the chapter by Markesbery and Ehmann.

#### **PREVALENCE OF DEMENTIA AND AD IN COMMUNITY STUDIES**

Prevalence studies of dementia and AD provide an important tool for understanding this age-related public health problem. In recent years, multiple studies have been performed in various locations worldwide. These studies allow comparison of data obtained from different populations. Although these comparisons can be used to generate new hypotheses, care must be taken in interpreting results since study differences may reflect disparities in methodology (design or case ascertainment) or differences in study site characteristics (institutionalization or survival rates) (38) rather than actual differences in cases. The use of death certificate data for case

ascertainment has not been practical as this is likely to identify only about one-quarter of the subjects suffering from dementia (39). The lack of biological markers or universally accepted criteria for what constitutes a case has posed the single greatest problem for prevalence studies of AD. Epidemiologic surveys have used a wide range of techniques for case identification. Even the use of similar strategies and instruments in different sites might not produce equivalent results owing to cultural diversity.

#### **Case Ascertainment and Diagnostic Criteria for Dementia and AD in Community Studies**

Overall, a significant part of the variation in prevalence reported in current studies is likely to be due to differences in methodology. The diagnosis of early dementia presents a particular problem in community studies and some investigators have chosen to report prevalence rates only for severe cases (40,41). In particular, the use of different criteria for diagnosing mild dementia can result in markedly different prevalence rates (42). A recent revision of DSM-III (DSM-III-R) (33), which includes some testing recommendations, may exclude a few mild cases since the tests recommended are not particularly sensitive in identifying early changes in cognition. Some authors have argued that mild cases are excluded by the DSM-III requirement that there be "loss of sufficient severity to interfere with social and/or occupational functioning." Evans et al. (43) have argued that this criterion is difficult to apply to a community study because "participants differ both with regard to the availability of family or friends and the sensitivity of these persons to manifestations of disease" (43, p. 2553). However, Hill et al. (44) found that a culturally adapted version of a functional scale developed by Pfeifer et al. (45) in southern California worked well in the Shanghai study. When the requirement for functional disability is waived, studies tend to have higher prevalence rates of dementia, but

it is unclear whether the very high prevalence rates of dementia and AD (approaching 48% at age 90) in the East Boston survey (43) can be explained by the investigators' decision not to require formal evidence of functional disability.

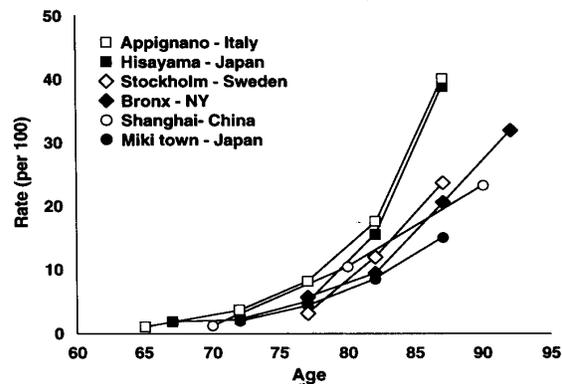
The most frequently used criteria for the diagnosis of AD are those developed by the NINCDS-ADRDA Work Group, Task Force on AD (2). These criteria specify deficits in two or more areas of cognition. Studies [such as the Framingham study (46)] that use the criteria established by Cummings and Benson (47) that require evidence of compromise in at least three spheres of mental activity might thereby eliminate milder cases and lower the prevalence estimation. Another approach that is likely to lower the prevalence rate of dementia is the identification of cases of dementia and AD from medical records (48), because even in a medically sophisticated community it is likely that some patients with dementia do not seek help from the physician; or, if they are being treated for other illnesses, the physician may not recognize that they have dementia.

In diagnosing dementing illnesses in the community, it is not always possible to carry out radiological and laboratory studies for economic and other reasons. Hence it is more difficult to rule out systemic or focal disorders that might present as dementia. This may lower the accuracy of the differential diagnosis of AD. The clinical differentiation of true vascular dementia from the so-called mixed cases--AD patients with a coincident stroke--has proven to be imprecise using either the Hachinski scale (49) or the Rosen et al. (50) modification alone, but Erkinjuntti et al. (51) have reported quite good clinical pathological confirmation when CT scans are also utilized to confirm the diagnosis. Thus, in the 1987 Shanghai survey, which did not include imaging procedures, the investigators chose to report age-specific prevalence rates for dementia, and have given an estimation of the percentage of such cases likely to be secondary to AD based on the clinician's examination (52).

## Age-Specific Prevalence Rates

The most consistent and robust finding in regard to the epidemiology of dementia is the exponential rise in prevalence as a function of age in the 65- to 85-year age range. This age-dependent relationship is independent of the definition of dementia used by investigators. It was first noted in two of the earliest community surveys of dementia, the survey of moderate to severe dementia in Syracuse, New York, based

**FIG. 1.** Prevalence of dementia in studies using DSM-III criteria. Symbols represent data from the following studies: □,



Rocca et al. (55); ■, Ueda et al. (58); □, Fratiglioni et al. (57); ◇, Aronson et al. (59); ○, Zhang et al. (52); ●, Fukunishi et al. (56).

on a random selection of subjects in specific census tracts, carried out by Gruenberg (53) in the late 1950s, and in a total population survey of severe dementia on the island of Sams, Denmark, carried out by Nielsen (54) at about the same time. This finding of an exponential rise in prevalence with age is also true of the most recent studies (52,55-61). Studies using DSM-III criteria for the diagnosis of dementia are plotted in Fig. 1.

Jorm et al. (38) used data from 22 studies carried out before 1985 to determine the coefficients for this exponential rise. Despite marked differences in overall prevalence, they reported that "the relationship between prevalence and age was found to be consistent. The problem with this model is that it predicts that everyone would become demented by age 100 or sooner depending on the exponential

coefficient. We know this is not true. Many centenarians are cognitively intact and quite vigorous. In the fall of 1980, Richard Meyer, a British businessman-philanthropist who was knighted on his 100th birthday, toured the United States at age 100 years and 6 months to raise money for his philanthropy, Concerts for Children. He lectured to the music faculties at Sarah Lawrence and Princeton, attended a number of fundraisers, and met with the National Endowment for the Humanities in Washington, D.C.--all within a 10-day period! Some centenarians even remain creative: Mary Robertson ("Grandma") Moses produced 25 of her masterpieces after age 100.

If the exponential or log relationship between age and dementia prevalence holds so well between ages 65 and 85, but not over the age of 85, what model should be used? Dewey (64) has suggested several other models including logit and probit models; we have plotted these various models in Fig. 3. We cannot distinguish between these models on the basis of existing data; community surveys of dementia in centenarians, including nursing home as well as community-dwelling subjects, need to be carried out.

There are, however, considerable data in regard to subjects in the 85-year age range, but these show marked differences in dementia prevalence among studies as is evident in Figs. 1 and 2. As those over age 85 represent the fastest growing segment of the United States population, these differences in prevalence rates would have significant public health impact for projections of social and fiscal costs of dementia (65).

In addition to the methodological problems that we have discussed as a possible explanation for these differences in prevalence rates, additional factors include the relatively small number of individuals in the over-age-85 samples as well as differences in local custom concerning institutionalization of the very elderly. But real cohort differences may exist; certainly differences among countries as to socioeconomic conditions and educational opportunities were greater at the turn of this century than they are today in regard to the

countries that have been surveyed.

The first study that specifically focused on 85-year-olds was reported by Skoog et al. (66), who surveyed half of all persons born between July 1, 1901, and June 30, 1902, and registered as living in Gothenburg, Sweden. Of the 783 living subjects selected, 37% refused either initial interview or follow-up examination. Of the remaining 494 subjects who underwent full evaluation, 29.8% met DSM-III-R criteria for mild, moderate, or severe dementia; thus 70.1% were nondemented. This is surely an underestimate of the prevalence of dementia in 85-year-olds considering that 275 declined to participate or come to the final evaluation. But even in the unlikely event that all of the noncompliant had been demented, at least 44% of the 85-year-olds were nondemented. Perhaps this survey sets useful limits on the prevalence of dementia at advanced age in a total community cohort.

### **Education, Occupation, and the Prevalence of Dementia**

In 1988, Mortimer (67) predicted that low education would be a positive risk factor for dementia in the very elderly. Zhang et al. (52) confirmed this prediction in the Shanghai across studies, with rates doubling every 5.1 years" (the 95% confidence limits were 4.79-5.37 years). We have found that the semilog plot used by Cross and Gurland (62) is very useful in visualizing this relationship since the exponential curve then becomes a straight line as shown in Fig. 2, which includes age-specific prevalence data from several recent studies using a variety of diagnostic criteria (38,43,46,52,55,59,63). The regression line, based on the Jorm et al. summary of the 22 earlier studies, fits these newest data remarkably well in regard to the age-prevalence relationship survey of dementia. Over one-quarter of that cohort had never received any formal education, and the prevalence of

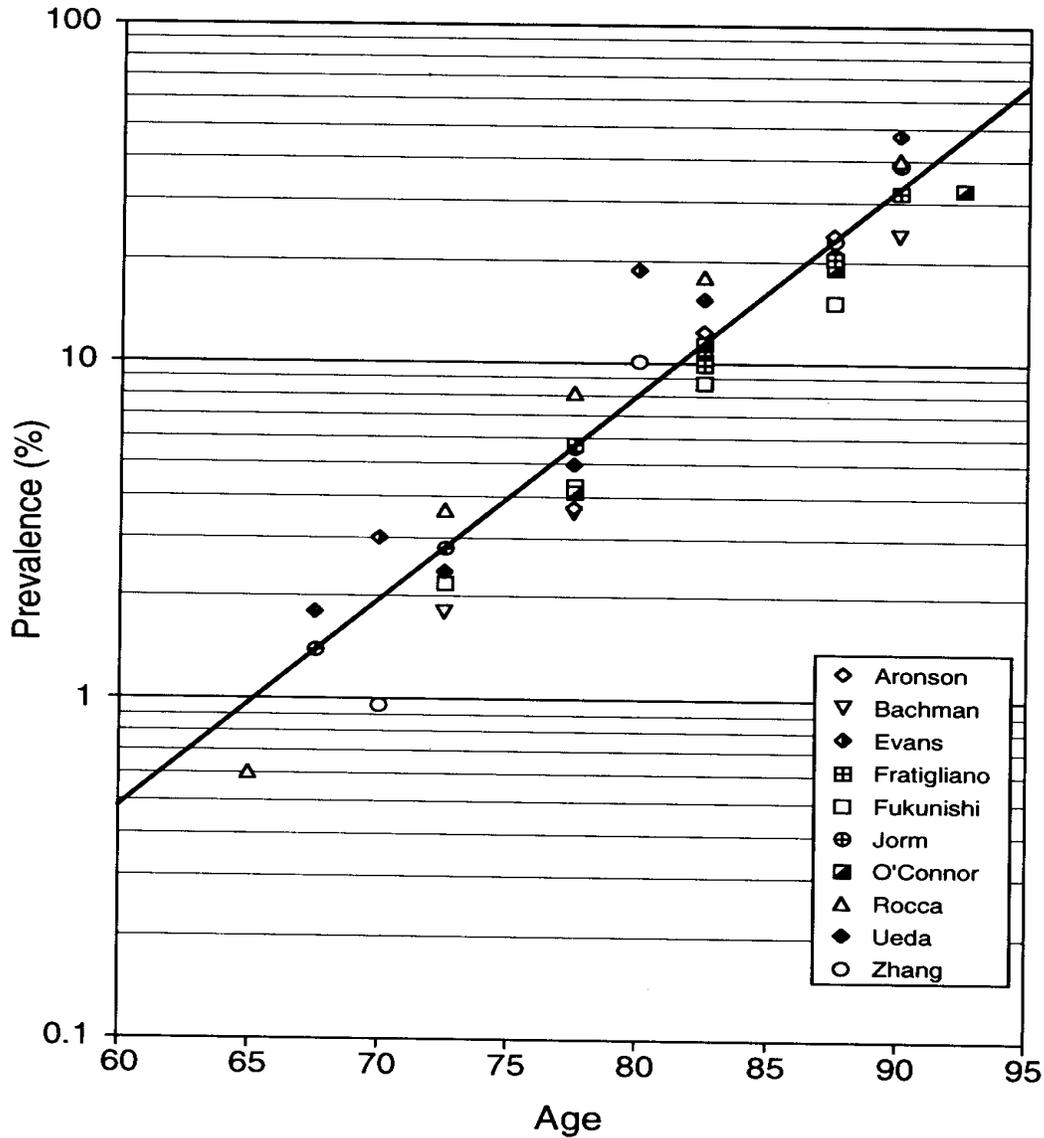
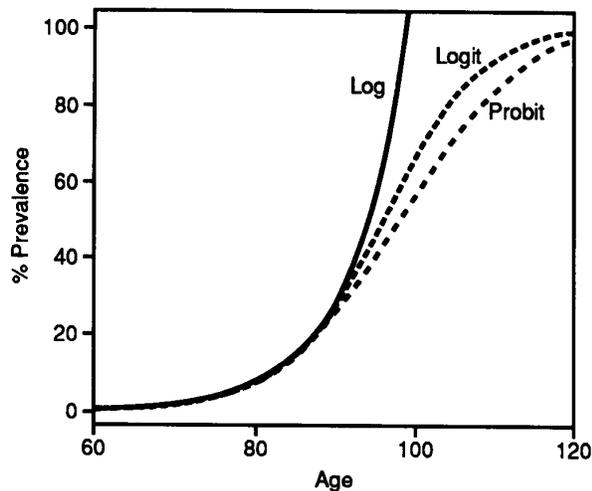


FIG. 2. Semi-log plot of prevalence data comparing the Jorm regression line with a number of recent studies (38,43,46,52,55-59,63)..

dementia *after age 75* (but not at earlier ages) was increased markedly in the uneducated. Although diagnoses of dementia were made clinically in these cases, the investigators were concerned that life-long impairment in cognition might have been misinterpreted as

dementia. Hill et al. (44) showed, however, that the education effect remained if algorithmic diagnoses based only on history and measures of instrumental activities of daily living, such as that of Pfeifer et al. (45), were made. That education is protective against



**FIG 3.** Comparison of log, logit, and probit plots of prevalence data from the studies that used DSM-III criteria.

functional impairment during aging has also been reported by Snowdon et al. (68) in their study of Catholic nuns over the age of 75. Since these initial reports, other studies have confirmed the effect of very low education (69,70).

In regard to occupation, there is now one case-control study in which subjects were matched for education (32) and two prevalence studies (55,71) that report a significantly increased prevalence of dementia in manual laborers. In addition, White et al. (72) have shown that low occupation is an independent risk factor for incident cognitive impairment in a longitudinal study, taking into account age, gender, education level, and history of stroke.

In contrast to the obvious effect of age and the very likely importance of education and occupation in regard to the prevalence of dementia and AD, the effect of gender is inconsistent. In many studies the prevalence rates for AD are significantly higher in women than in men, whereas the prevalence rates of vascular dementia are sometimes higher in men. Heyman et al. (73) reported an increased prevalence of dementia in black women, but no gender differences among white subjects. In the Shanghai survey (52) a logistic regression that included age, education, and gender showed that female gender was an independent

predictor of dementia. It is, however, uncertain how much of this effect is due to differential longevity of demented women. For example, in the Framingham prevalence study (46), the female/male ratio for cohort members 75 years of age and older was 1.8 for all dementia and 2.8 for AD. But in the Framingham incidence study (74), there was no gender difference in incidence of dementia or AD, leading the investigators to attribute their prevalence findings to differential survival after onset of dementia. In Japan, where the frequency of vascular dementia is greater than AD, men were found to be at a greater risk. Thus, in the Ueda et al. (58) survey the ratio of women/men was 1:2, but in the Fukunishi study there was no gender difference. In addition to differences in longevity, there are differences in education between men and women in many of these cohorts, which might confound the gender difference if not included in the analysis.

### Other Demographic Factors and the Prevalence of Dementia

Many basic issues regarding the prevalence of dementia and AD are still indeterminate. These include potential racial differences and urban/rural differences. Although a preliminary study in Nigeria suggested a relative absence of dementia in black populations (75), studies in the United States report higher rates for black subjects than for white subjects (41,73). Although some 1960s studies of purely rural communities had significantly lower rates than other studies [e.g., Akesson (76)], these rate differences might be due to differences in methodology or to the employment of total population assessment. The latter could explain the results since even in urban studies, total population surveys tend to have lower rates than studies that examine only a random sample (38). The prevalence of dementia was not lower, however, in the total community sample in the village of Appignano in Macerata Province, Italy, a very rural area (55). A better understanding of these issues will undoubtedly emerge from studies currently in progress.

## The Relative Prevalence of AD and Vascular Dementia

In the clinical setting, the diagnosis of probable AD based on the NINCDS/ADRDA criteria is a highly accurate one. In the community, however, there is a greater likelihood of coincident factors that increase the difficulty of diagnosing AD. Two of the major factors are alcoholism and cerebrovascular disease. Because in many populations elderly males are particularly prone to strokes, the differentiation of a concurrent stroke in AD patients and vascular dementia is often unsatisfactory. Two frequently used tools for the diagnosis of vascular dementia, the Hachinski ischemic index (49) and the Rosen (50) modification of the Hachinski index have been shown by Rosen et al. not to differentiate vascular dementia from mixed AD and vascular dementia (50,51). Surprisingly large differences have been observed among community studies in regard to the proportion of subjects diagnosed as having AD or vascular dementia (77). Studies from Japan (56,58,78) show a preponderance of subjects diagnosed as vascular dementia. In contrast, 84% of the subjects in the East Boston study (43) were felt to be suffering from AD. In a study of randomly selected 85-year-olds in Gothenburg, Sweden, Skoog et al. (66) based their differential diagnoses of dementia on both patients and informant interviews using DSM-III-R and NINCDS/ADRDA criteria for dementia and AD, respectively, and the Erkinjuntti criteria for vascular dementia, the latter incorporating information from CT scanning and neurological history for the diagnosis of vascular dementia (51). The diagnosis of vascular dementia, made in 46.9% of the cohort, was more common than the diagnosis of AD (43.5%); the 8.2% of cases with a diagnosis of "mixed" dementia was included among the vascular cases. There were no significant sex-related differences in prevalence or severity.

## THE INCIDENCE OF DEMENTIA

Although numerous prevalence studies of dementia and AD have been conducted, estimates of the incidence (new cases in a specified period) of dementia and AD are very limited (59,74,79-82). Since it is possible that life expectancy for demented individuals differs among societies, one might hope that incidence studies would narrow the variability found among prevalence studies. Moreover, virtually all risk factor studies have been conducted using the case-control paradigm, whereas ideally incident cases should be utilized to determine risk because the former may identify conditions associated with disease longevity rather than the actual risk of developing disease. Most important, when exposure history is obtained prior to the development of disease, it is unlikely to be subject to the bias of selective recall. Methodological problems afflict incidence as well as prevalence studies. The ability to compare incidence rates at different study sites is dependent on similar design, screening, and diagnostic procedures. However, during the past several years, a number of community-based incidence studies with similar designs have been initiated, and within a few years the data should become available.

The same methodological problems involving sampling and case ascertainment that occur in prevalence studies also pertain to longitudinal studies. Two additional possible confounds may occur. In most longitudinal studies there are a significant number of dropouts between evaluations (an exception being the Lundby study, which maintained a 98% participation rate); since individuals developing symptoms of dementia may preferentially choose to discontinue participation, the incidence of dementia might be underestimated. Another possible confound is the differential mortality of dementia patients. This is especially important in regard to studies with long intervals between evaluations such as the Lundby and Shanghai studies. In the Lundby study, in which evaluations were carried out at 10- and 15-year intervals,

the investigators interviewed families of those who had died in the interim in regard to the status of the subjects, but the validity of this procedure is uncertain. In the Shanghai survey of dementia in which part of the cohort was reevaluated after 5 years, the investigators will use analytical approaches to estimate cases of dementia that may have developed in those who died between evaluations.

From the few available studies the incidence of dementia rises sharply with age over the span of ages between 60 and 85 years. In the Bronx Aging Study, the annual incidence of dementia reached 6% in those over age 85 (59), but in the Lundby study there appeared to be an actual drop-off in rate after age 90 to below 290 (79). Differences in incidence rate between these studies are to be expected because they used very different designs, evaluations, and criteria, but the difference in age trends is unsettling. An annual incidence of dementia of 1% per year in those 70 to 79 years old was reported in the Lundby study (82), but a similar incidence rate was observed in the Bronx (59) and Framingham (74) studies at ages 75 to 80 and at ages 75 to 84 in the Liverpool study (81); an incidence of 3% per year was observed in those 80 to 84 in the Bronx study and in those over 85 in Liverpool. These discrepancies are quite significant and their resolution must await data from current ongoing longitudinal studies.

### Longitudinal Studies of Dementia

Because of the importance of the data derived from these studies, several of the major studies, completed or ongoing, are described.

*The Lundby study* was the first longitudinal analysis of dementia. In this study of a total population from a geographic area in Sweden, 2,612 persons were prospectively followed by Hagnell and associates (79,8286) over a 25-year period. Examinations were conducted in 1947, 1957, and 1972. Evaluations were based on informant interviews, subject interviews, and observations of subjects; however, formal mental status and neuropsychological and neurological examinations were not carried

out. Initially, the subjects were described in terms of "age psychosis" and "arteriosclerotic psychosis," but have been reclassified by Rotsman et al. (82-84) in terms of AD and vascular dementia. Incidence rates per year of developing AD or MID were calculated. The lifetime risk of developing AD was calculated at 25.5% for men and 31.9% for women, although rates for men were slightly higher than for women until age 80. Multi-infarct dementia was more common in men (29.8%) than in women (25.5%). Additional analyses of family history and other risk factors are in progress.

*The Baltimore Longitudinal Study of Aging (BLSA)* is a prospective study of normal aging that has been conducted since 1958. Initially limited to men, enrollment of woman began in 1978. The effort has included more than 1,900 subjects and is now part of the Ger-ontology Research Center of the National Institute on Aging.

An initial study of dementia in this cohort was conducted by Sluss et al. (80), who performed chart review of active BLSA male participants and estimated the incidence of AD to be 3.2 per 100 person years at age 80. Since there may be a tendency for men with AD to withdraw or fail to return for examination, the inclusion of only those subjects who were active in the study could result in underestimation of the probability of developing AD. In addition, diagnosis of dementia was determined by review of information available from BLSA research charts rather than examinations with appropriate laboratory studies. Follow-up of the BLSA subjects diagnosed with dementia was reported by Arenberg (87), who found that 22 of the 27 cases were performing well on cognitive tests concurrently or several years after the presumptive diagnosis, suggesting possible misclassification.

A new effort using NINCDS/ADRDA criteria for AD is currently under way in the BLSA. A survey of deceased participants is being included along with examination of active and inactive subjects. This approach will allow the examination of risk factors such

as head trauma without case recall bias.

*The Framingham study* (46,74) began with a general population sample in the town of Framingham, Massachusetts, in 1950. There were 5,209 men and women aged 30 to 62 initially enrolled and followed every 2 years with the primary focus on risk factors for cardiovascular diseases. In 1976 and 1978 a brief screening examination was carried out by a neuropsychologist at which time the cohort included 2,828 subjects. Beginning in 1982 the Mini-Mental State Examination (MMSE) was administered at each biannual examination and detailed evaluations were carried out on those below education-computed MMSE cutoff scores. Patients diagnosed as demented were classified as mild, moderate, or severe, but prevalence and incidence figures were limited to those with moderate or severe dementia based on functional criteria.

*The Bronx Aging Study* (59,88,89) began in 1980; 488 nondemented subjects, ages 75 to 84 years, were recruited. The study was unique at the time in that each subject received both an intensive medical and an intensive dementia workup, the latter including neurological and neuropsychological evaluations on an annual basis. Multiple laboratory tests both for cardiovascular disease and dementia, the latter including brain imaging, were carried out as indicated. Diagnoses of dementia were based on DSM-III and NINCDS/ADRDA criteria. However, this was a volunteer rather than a population sample and is subject to self-selection bias. In particular it is likely that a few subjects joined the study because of their perception of early memory problems, and, although the subjects selected tested within normal limits at entry, this may have enriched the sample with subjects at risk for dementia. As we have already noted, an opposite bias may exist in population samples in which there is often a high dropout rate that may be enriched with subjects undergoing cognitive changes who no longer wish to participate in neuropsychological testing.

*The Shanghai Survey of Dementia* began in 1987 when 5,055 randomly selected residents, age 55 and over, living in the Jing-An district

of Shanghai were sampled by neighborhoods, based on a randomized cluster sampling technique developed by Levy et al. (90). Oversampling of the elderly was accomplished by screening individuals age 55 and over in one-third of the randomly selected neighborhoods, individuals 65 and over in one-third, and individuals 75 and over in one-third. During the screening interview, demographic data and a medical history were obtained from the subject or from an informant, and a Chinese version of the Mini-Mental State Examination (CMMS) was given to the subject (90,91). The 510 subjects who scored below education-adjusted CMMS cutoff scores together with a stratified 5% sample of those who scored above these cutoff scores underwent an intensive clinical evaluation that included a medical history and physical examination, a neurological examination, a psychiatric interview, and a variety of standard psychiatric, neuropsychological, and functional scales that had been adapted to the Shanghai cohort. Dementia was diagnosed on the basis of the DSM-III criteria (1) and AD on the basis of the NINCDS/ADRDA criteria (2). A second screening and evaluations of subjects age 75 and over was carried out in 1988, and the entire living cohort was reevaluated in 1992. The 1992 survey is now being analyzed and will provide incidence and risk factor data on this cohort. The sample differs dramatically from Western samples in terms of life-long socioeconomic conditions--for example, 27% of the sample had received no formal education what-so-ever--but it represents a true community sample with a very high compliance rate.

*Liverpool:* In the mid-1980s Copeland et al. (81) studied a cohort of 1070 community living persons aged 65 and over using the Geriatric Mental State (GMS) interview that they had developed, together with a computerized algorithm (AGECAT) for making diagnoses. Three- and six-year follow-ups were obtained, and the incidence of dementia was calculated based on the 3-year follow-up with diagnoses confirmed at year 6. They report an incidence for all dementias of

0.38 per 100 person years at ages 65 to 74, 1.18 per 100-person years at ages 75 to 84, and 2.87 per 100-person years in those age 85 and over.

*EURODEM*: From numerous studies being conducted in Europe, six studies have been designated as EURODEM incidence studies: PAQUID (Bordeaux, France), Italian Longitudinal Study of Aging, Rotterdam Elderly Study (Netherlands), Zaragoza Study (Spain), Multicenter Study of Cognitive Functioning and Aging (United Kingdom), and Alpha Study (Liverpool, UK). To minimize methodological differences, a core protocol was adopted. It includes (a) two assessments of the population, at least 2 to 3 years apart; (b) sample size >4,000; (c) inclusion of community and institution dwellers; and (d) a two-phase case-finding procedure with common screening and diagnostic methods. Collaborations of this type will allow effective comparison of the rates and risk factors derived from these different studies over the next decade.

## MORTALITY

The evidence that dementia shortens life expectancy goes back to the classic 1955 study of Roth (92), who demonstrated that survival was markedly shortened in elderly mental hospital inpatients with "senile psychoses" and "arteriosclerotic psychoses" as compared with inpatients with depression or schizophrenic disorders (paraphrenia) of the elderly. Wang and Whanged (93) in the early 1970s summarized a number of clinical studies of subjects with AD and Pick disease; subjects with presenile dementia of the AD and Pick type lived on the average 6.8 years as compared with expected survival of 21.5 years; those with onset in the senium, 5.1 years versus the expected 9.6 years; and those with arteriosclerotic brain disease, 3.8 years versus the expected 14.0 years. In a later clinical series, Barclay et al. (94) reported longer life expectancies from onset of 8.1 years for dementia of the Alzheimer type and 6.7 for MID, but again with a major reduction in

expected survival. Similar findings have been reported in other recent series (95). In a cohort of 323 patients who had been referred to an outpatient department because of suspected dementia in the early 1980s, 49% of the AD patients and 63% of those with vascular dementia had died in 1989 compared with 1.7% of those with functional memory problems (96). In this study, mean survival using life table analysis with the product limit method showed that survival from symptom appearance was 10.3 years in AD and 8.0 years in MID. The authors suggested that life expectancy of dementia patients has increased over time but remains significantly different from that of nondemented individuals.

Available community studies confirm the malignancy of dementia. Nielsen et al. (54,97) identified all cases of severe dementia on the island of Sams, Denmark; 5 years later none of these subjects was alive, in contrast to individuals with depression or without cognitive impairment who had a much better survival. Evans et al. (98) studied mortality in the follow-up study of East Boston subjects, using the Cox proportional hazard model to adjust for age and gender. There was a significant increase in risk of death conferred by AD, but the odds ratio was only 1.4. This risk increased in patients showing debility from AD. A much greater effect of AD and vascular dementia on 5-year survival was observed in the Shanghai study (99).

These investigators used a multivariate analysis, the Cox proportional hazard model, to determine the relative risk of dying based on 5-year vital data obtained on the 3,153 subjects age 65 and older who participated in the 1987 population survey of dementia in Shanghai, China, taking into account not only age, gender, and education level but also 15 prevalent medical conditions reported in the initial 1987 survey. The mortality risk ratio was 5.4 (95% CI = 1.4-14) for AD and 7.2 (95% CI = 3.6-14) for "other dementias" (a category that included predominantly vascular dementia), similar to the mortality risk ratio of cancer (RR = 5.5; CI = 2.9-11) in those aged 65 to 74. In those aged 75 years and older the

mortality risk ratios were 2.7 (95% CI = 2.1-3.6) for AD and 3.5 (95% CI = 2.54.8) for "other dementias." In those aged 75 and older the population attributable risk of death due to the dementing disorders was 20.5%. Thus, both AD and vascular dementias were truly malignant. Certainly, in this population these dementing disorders constituted a major risk factor for death in the elderly over age 75. If similar figures held in Western countries in which life expectancy is about 76 years, then 10% of *all* deaths would be attributable to the dementing disorders.

### **RISK FACTORS FOR AD AND CAUSALITY**

Do the putative risk factors for dementia and AD that we have discussed meet accepted epidemiological criteria for causality (100)? These criteria include strength of association between risk factor and outcome, consistency between studies, a dose-response relationship, appropriate temporal relationship, and biological plausibility. This section considers which of the risk factors we have discussed meet these criteria and can be causal, and to what extent these putative factors account for existing cases of AD.

Family history has been consistently demonstrated to be a risk factor for AD. Many excellent studies in this regard have concentrated on the question of whether the familial association is genetic. This is no longer at issue since specific point mutations on the amyloid precursor protein (APP) gene of chromosome 21 have been identified in a small subset of early-onset AD (101-103). Within the past year linkage studies have identified additional gene loci on chromosome 14 (104-107), accounting for the majority of early-onset kindred. There is also evidence for linkage to a chromosome 19 site in late-onset cases (108). See also the chapters by Bird and St. George-Hyslop.

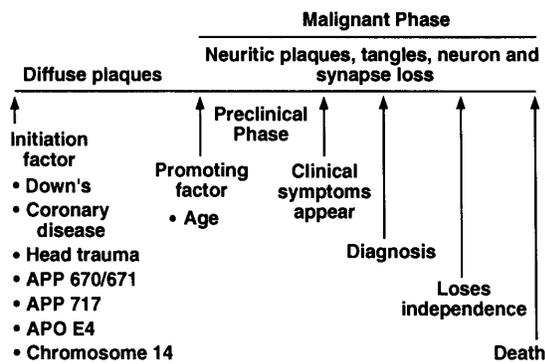
It has been argued by some geneticists that a large proportion of AD patients are due to a gene (now, genes) with an incomplete but age-dependent penetrance (109,110). However, the

relative difficulty recently encountered in finding large numbers of families with strong autosomal dominant pedigrees and the discordance observed in many identical twin pairs (111113) are inconsistent with this concept. On the other hand, a positive family history of AD

(that is, a history of AD in a single first-degree relative) meets the epidemiological criteria of causality: a strong association (relative risk between three- and fourfold), consistency among studies, appropriate temporal relationship, a relationship between the degree of exposure and the disease (a "dose-response"), and biological plausibility (the APP mutations).

Increasing evidence is accumulating that head injury meets the epidemiological criteria of a causative factor for AD. In a recent and meticulous case-control study, Graves and associates (16) found that head trauma leading either to concussion or a visit to a doctor was strongly associated (relative risk greater than threefold!) with subsequent development of AD. Graves et al. note in their review that there has been striking consistency in regard to the strength of association between head injury and AD among case-control studies, whereas much lower ratios were found in one retrospective and in one prospective longitudinal study. The EURODEM reanalysis (17) confirmed the strength and consistency of this association. The key issue is whether recall bias can account for the increase in history of head trauma in the case-control studies, where the concerned informant or family may often have reflected on past events and selectively recalled more events of head trauma, as compared with the number of events of head trauma recalled by controls or by the informants or families of the controls.

Katzman (69) has recently reviewed the available data in regard to the protective effect of education shown in Table 2. It is evident from the data in this table that there is a consistent and significant effect, with a risk ratio of about 2, when noneducated are compared to those with more than 6 years of schooling. In the Shanghai survey a risk ratio



of 4.9 was found for the development of clinically diagnosed AD when noneducated are compared to those with more than 6 years of schooling. A lesser effect, that does not reach significance, is present when those with elementary education are compared to those with secondary schooling.

### BIOLOGICAL PLAUSIBILITY

In regard to biological plausibility, there have been many advances in our understanding of the cellular and molecular basis of AD. There is a good agreement that the final cellular event that leads to cognitive impairment is loss of neocortical and hippocampal synapses (115-118). One plausible hypothesis in regard to low education as a risk factor is that noneducated individuals have a reduced brain reserve (51,67) probably due to a lesser synaptic reserve (69).

But in regard to which of the many molecular and cellular changes that occur prior to synapse loss are the critical ones, there is now strenuous debate as indicated in this book in the chapters by Terry et al., Davies, Cotman and Pike, and Robakis. The essence of this debate centers around the etiological role of amyloid. At the current stage of knowledge, one can argue that the epidemiological data is most easily interpretable if *diffuse*  $\beta$ -amyloid containing plaques do play a central role. In individuals with Down syndrome, a condition in which AD pathological changes occur uniformly in the brain by age 40 and in which the pathology is attributed to the additional genes resulting from the triplication of

chromosome 21, including the APP gene, *diffuse*  $\beta$ -amyloid-containing plaques in neocortex (defined as focal collections of  $\beta$ -amyloid without neuritic involvement) are present in the brain as early as age 10 (119), 20 to 30 years before the development of the full panoply of AD changes observed in the Down brain. The known familial AD (FAD) mutations at codons 670/671 and 717 on the APP gene flank the  $\beta$ -amyloid sequence and are consistent with this mechanism. The core of the neuritic plaque contains, in addition to  $\beta$ -amyloid, other proteins, sometimes termed chaperone proteins, that are thought to participate in the conversion of soluble  $\beta$ peptide to  $\beta$ -amyloid; these include  $\alpha_1$ -antichymotrypsin, complement, and apolipoprotein E (ApoE) (120). Promoters for APP include *c-fos* and heat shock proteins. Genes for  $\alpha_1$ -antichymotrypsin, *c-fos*, and one of the heat shock proteins are located on chromosome 14 near the chromosome 14q24.3 marker for the early-onset familial cases. The gene for ApoE is located on chromosome 19 near the marker for the late-onset FAD marker.

Recently, ApoE alleles were studied in autopsy-confirmed AD patients from 30 families with multiple affected members (28 had late onset, after age 60) and in nondemented controls. There was a higher frequency of ApoE4 in AD (52%) than in nondemented controls (16%),  $p = .01$  (121). ApoE4 also bound soluble  $\beta$ -amyloid peptide more avidly than did ApoE3; antibodies to ApoE stain amyloid deposits in AD and other amyloidoses (120,121). Roses et al. (122) have found that the ApoE4 allele is present in over 65% of the cases with late-onset FAD and 50% of the cases of sporadic AD with onset between ages 65 and 80, whereas it is present in only 30% of controls. This may represent a major finding, although it needs to be replicated. These investigators reported that the ApoE4/E4 allele that is normally present in 3% of the population increases the odds of getting AD sevenfold; the ApoE4/ E3 allele, which is present in 23% of the population, increased odds 3 to 4 times. If so, one might speculate that over 30% of the cases of AD

with onset between ages 65 and 80 could be attributed to the ApoE4 allele. If the effect of ApoE4 is due to its avid complexing with the soluble  $\beta$ -amyloid peptide, then it is possible that the three genes involved in familial AD all act through a single mechanism involving  $\beta$ -amyloid, but there is no direct evidence for mutations in any of the candidate genes on chromosome 14.

In addition to a possible relationship between genetic factors and amyloid, diffuse  $\beta$ -amyloid plaques occur in relationship to two of the other putative risk factors that we have described, head trauma and myocardial infarct. Head trauma might act by production of diffuse

**FIG. 4.** AD as a chronic disease: cancer model.

plaques as occurs in Down syndrome. The promoter region for the  $\beta$ -amyloid precursor protein (APP) gene contains "heat shock" promoter elements that could be activated by such insults as trauma, anoxia, and alcohol as well as a *c-fos* promoter element that could be activated by these and other stress events leading to the production of excessive amounts of APP and an increase in its degradation to  $\beta$ -amyloid with the development of  $\beta$ -amyloid-containing diffuse plaques. In some cases the brains of boxers with dementia pugilistica have been found to contain neocortical diffuse plaques in the typical Alzheimer pattern (123) in addition to the neurofibrillary tangles that are present in a subcortical distribution in these brains. Recently it has been reported that one-third of young adult subjects dying within 3 years of a serious head injury have diffuse plaques in their brain.

In their longitudinal study of 75- to 85-year-old nondemented volunteers, Aronson et al. (89) found that myocardial infarct was a risk factor for dementia, in elderly women in particular. Although this has been found to be a risk factor in only one study, the report is of interest because Sparks et al. (124) have found that in autopsies of older individuals who died

without dementia but who had over 75% constriction of a coronary vessel, there is a marked increase in the number of diffuse plaques in the brain as compared to age-matched individuals who did not have severe coronary disease.

#### **EPIDEMIOLOGY OF AD: A PUBLIC HEALTH PERSPECTIVE**

The epidemiological evidence that AD will become increasingly the dominant disorder in late life--both in terms of its increasing prevalence as the population ages (65), and the recent advances in identifying risk factors in AD--may have widespread social impact. If the sum of the evidence in regard to risk factors presented above is correct, we may already know as much about the major risk factors for AD as is known about risk factors for other major chronic diseases, such as myocardial infarct and cancer. But in regard to our understanding of these putative risk factors, there are also major reservations. The question of what proportion of cases are associated with family history can more directly be addressed by the epidemiological evidence. The risk of developing AD is increased three- to fourfold if one has a first-degree relative with the disorder. From a population perspective, it becomes possible to calculate the "attributable" risk, knowing the frequency of the risk factor in the matched, non-affected population and the relative risk or odds ratio. Mortimer (125) calculated the attributable risk due to family history as 26%; that is, in the groups studied 26% of all AD cases could be attributed to probable genetic factors. In regard to head injury (with concussion), using the relative risk reported in the EURO-DEM reanalysis (18), the attributable risk due to head injury is about 5% to 7% of cases of AD. This risk is most straightforward in those with onset of AD before age 75.

In the elderly, those in whom AD begins after the age of 75, the data on the risk factors are not as certain as in those with onset at earlier ages. In particular, the role of family history in this cohort is difficult to evaluate, in part because mothers and fathers often died at

an early age. Also, the number of case-control studies in this age group has been limited. From the sparse data available, head trauma appears to play a significant although lesser role, perhaps because the number of cases per year due to head trauma remains fairly static while the total number of cases rises exponentially with age, relegating this risk factor to a lesser role. In this older age group however, lack of or low education becomes a highly significant risk factor, now meeting all of the Bradford-Hill criteria. And in the very elderly, with onsets for the most part after age 80, there is evidence from a single study that myocardial infarct may be a risk factor (89). In the Bronx Aging Study, myocardial infarct increased the risk of AD threefold among elderly women and accounted for 20% of the cases of AD in this group. There was also an increase in risk among elderly males but this did not reach significance possibly due to the sample size. If this risk factor could be extrapolated to the general population, it would account for another 10% to 15% of the attributable risk, but the finding needs to be confirmed by other studies of the very elderly.

If these risk factors are simply additive at the population level, family history and head trauma together would account for 31% of the attributable risk for AD and when an additional 10% to 15% is added due to the attributable risk from coronary heart disease in elderly women, 41% to 46% of the attributable risk for AD may be known. And this does not take into account the cases due to low education. By way of comparison, the attributable risk of heart attacks from obesity, high cholesterol, lack of exercise, and diabetes together is about 40%!

### **AD AS A CHRONIC DISEASE**

The foregoing epidemiological and biological advances suggest a view of AD as a chronic disease in the sense that the term is used by epidemiologists to describe atherosclerotic heart disease and cancer. The picture emerging is that of a long preclinical period, a period in which intervention to

prevent the development of dementia may be possible. Perhaps decades before the onset of clinical symptoms, as initiating factor, the diffuse plaque, is laid down as the result of genetic, traumatic, anoxic, and perhaps other events (Fig. 4). At some point the intracellular events leading to neuritic degeneration, neurofibrillary tangles, and synapse loss begin, perhaps due to the action of the  $\beta$ -amyloid itself, but very likely requiring a different and not yet understood promoting factor(s).

At this point the AD changes may be conceived to have entered a malignant phase and continue to progress on their own, leading to the irreversible decline that is the tragedy of AD. Clinical symptoms begin to appear when the number of synapses falls below a threshold level or when acute stressors exceed the brain's capacity to respond effectively. It is at this stage of the pathogenetic process that it is likely that lack of education and perhaps later life cognitive inactivity play a role by decreasing synaptic reserve. This concept is illustrated in Fig. 4.

There are still many uncertainties in regard to the evidence at hand. The assumed central role of amyloid is in dispute. Putative factors need to be confirmed prospectively. If it turned out that the head trauma effect were largely or entirely due to recall bias, much of the preceding argument would be meaningless. Similarly, the effect of myocardial infarct is based on only one epidemiological and one pathological study. It is critical that these weaknesses be addressed, particularly in the context of longitudinal studies carried out on community samples or well-defined cohorts in which the history of exposure to putative risk factors is obtained in detail before the development of dementia. If this overall picture proves to be correct there are important societal implications.

## Alzheimer's Disease

**TABLE 2.** Effect of no or low education on prevalence of dementia and AD

	Survey population		Diagnostic criteria	Number demented	Illiterate vs secondary +	Primary vs secondary +
	N	Age				
Shanghai (52)	5,055	55 +	DSM-III for dementia	159	2.981' (<.0001)	1.291' n.s.
			NINCDS/ADRDA for AD	107	4.80t (<0.0001)	1.71t n.s.
Bordeaux (60)	2,792	65 +	DSM-III for dementia	101	1.94tt (<0.0008)	1.09tt (0.02)
Stockholm (57)	1,810		DSM-III-R for dementia	216		1.94'(<0.001)
			DSM-III-R for AD	109		1.47* n.s.
Appignano (55)	779	60 +	DSM-III for dementia	48	7.2% of illiterate, 0.5% of >5 yr	2.8% of 5 yr+, 0.5% of >5 yr
Finland (40)	8,000	30 +	Modified DSM-III to exclude mild dementia	163	Illiterate > secondary	Primary < secondary
Ashkelon (70)	1,399	75 +			Illiterate > secondary	Primary > secondary
Cambridge, England (114)	2,302	75 +	DSM-III using CAMDEX	242		1.31 n.s.**

Modified from Katzman (69).

tOdds ratio in entire cohort of 5,055 determined by logistic regression; terms included diagnosis, age, education, and gender. ttRelative risk determined by use of Cox model, including age (60).

\*Odds ratios calculated from data in reports, using the Mantel-Haenzel statistic.

\*\*Demented subjects who left school prior to age 15 compared to subjects with longer education.

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# Alzheimer's Disease: The Genetics of Risk

ALLEN D. ROSES *Duke University*

**Each copy of an  $\epsilon 4$  allele of the gene encoding the lipid carrier apoE increases the probability of the disease and shifts its onset to lower ages. Yet the gene does not cause the disease. Thus, although genotyping is highly valuable in diagnosis and drug testing, it cannot offer useful predictions about persons whose cognition is unimpaired. After discovery of a second susceptibility gene, predictability will change profoundly.**

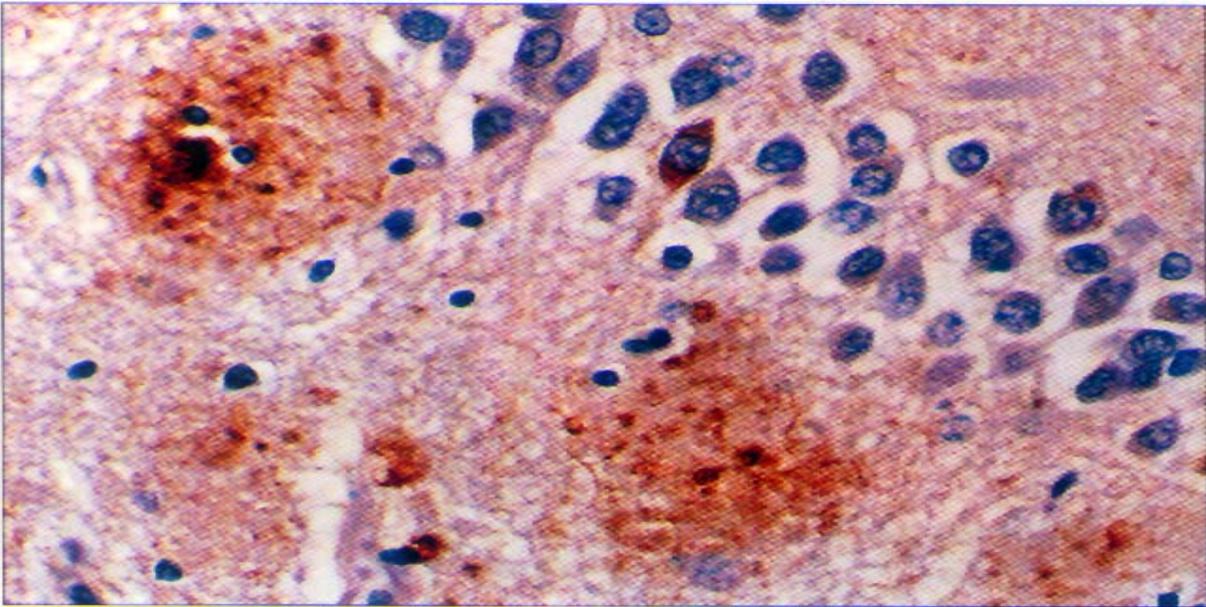
Among the difficulties encountered in hunting disease-related genes, one of the most vexing is that of discerning between harmful and harmless variations in DNA. A harmful version is termed a mutation, while the rest are taken to be polymorphisms, occurring without obvious phenotypic effect. The latter may seem to have entered the genome solely as landmarks enabling researchers to make genetic maps. Yet the most common human diseases may represent the combined actions of variable traits over long spans of time. As a population ages, these diseases can become prominent, perhaps especially in the brain, where the heterogeneity of neurons and the intricacy of their function may help to bring subtle, slow-developing metabolic abnormalities to the forefront in one or another neuronal population.

An example is the dementia of Alzheimer's disease, which affects an estimated 3 to 4 million patients in the United States alone. Mutations in any of three genes are considered deterministic: They can cause the disease as an early-onset autosomal dominant condition (defined as becoming evident by age 60, and sometimes before age 40). Although the penetrance may be incomplete and the actual age of onset highly variable, the risk distributed among the children of persons with such a mutation approaches a mendelian 50%, and in a person confirmed to have the mutation the risk

approaches a certainty. A fourth gene has an entirely different character. While the others affect a minute proportion of the human population--families known to carry a deterministic mutation number only about 120 worldwide--variations of the fourth gene are carried by everyone. And while the other genes permit accurate identification of risk or absence of risk, person by person, the fourth gene permits only estimates of relative risk of late-onset, or sporadic, Alzheimer's disease for the six genotypes arising from the gene's three alleles.

The fourth gene codes for apolipoprotein E, a lipid carrier best known for its intensively studied influence on the pathogenesis of cardiovascular disease. In the brain, the various *APOE* genotypes affect the rate of a lifelong, universal metabolic process perhaps entirely different from what apoE mediates in the periphery--- process that would make the Alzheimer phenotype ubiquitous, despite even the "safest" genotype, if everyone lived to be old enough. The status of *APOE* as a susceptibility polymorphic locus

Dr. Roses is Jefferson-Pilot Corporation Professor of Neurobiology and Neurology and Director, Joseph and Kathleen Bryan Alzheimer's Disease Research Center, Duke University School of Medicine, Durham, N.C. This is the seventh in a series of articles on the clinical impact of genetics research.



**Figure 1.** Amyloid plaques and neurofibrillary tangles at specified densities in sectioned brain tissue constitute the neuropathologic criteria confirming Alzheimer's disease. Here both plaques and tangles appear in the hippocampal dentate gyms of an Alzheimer patient. The plaques (stained reddish brown) are extracellular lesions best known for their content of the amyloid peptide  $A\beta$ . More than 30 other proteins have also been found. The tangles (stained blue) are intraneuronal bundles of paired helical filaments consisting perhaps entirely of protein tau, which normally stabilizes the cell's microtubules. The plaques may occur in the absence of dementia, while the tangles are seen in illnesses other than Alzheimer's disease. Moreover, the neuropathology is known---indeed, definitive of Alzheimer's disease-- only after the patient's death, often long after the onset of dementia. In consequence, the relation between the pathology and the actual mechanism of the disease remains unclear (Micrograph courtesy Christine Hulette, Duke University)

rather than a deterministic mutation means that in normal persons, a test for genotype has no useful predictive power. Although lifetime probabilities will differ, depending on genotype, no one is immune to Alzheimer's disease, and no one is certain to get it. Hence, in the absence of a preventive strategy, identification of a high-risk inheritance can only cause fear, and perhaps place the individual in peril of discrimination by employers, insurers, or governments.

For the differential diagnosis of a patient presenting with cognitive impairment, the situation changes. In this setting, identification of a high-risk *APOE* genotype can raise the likelihood of Alzheimer's disease to greater than 95%. For testing of possible therapies, genotyping may likewise be valuable. It facilitates the identification of specific efficacy or may help to reveal that a drug is ineffective. Indeed, therapeutic trials may now be

impossible without genotyping. In any event, the genetics of risk of Alzheimer's disease is about to undergo change. A second susceptibility gene, situated on chromosome 12, will soon be discovered, with profound implications for the ethics of screening.

### *Plaques and Tangles*

At present, a diagnosis of Alzheimer's disease can be considered definitive only if brain tissue can be mined. Certainly, the initial stages of the disease are subclinical and slow. In fact, recent evidence suggests altered brain function, in the form of decreased glucose metabolism, at least two decades before symptoms would be expected. Thus, the genetic factors promoting or causing the disease appear to be long-smoldering.

At some point, a cognitive deficit becomes

evident. The course thereafter is of gradually worsening forgetfulness, decreasing attention span, and mood alterations, often including frustration and agitation. Eventually, the pathogenetic events may come to constitute an autocatalytic cascade no longer dependent on a genetic trigger. At this point, the dementia tends to accelerate, in tandem with brain atrophy. Age of clinical onset is notoriously difficult to establish, but if possible Alzheimer's disease progresses to probable disease, it usually does so within a year. By then, cortical atrophy is usually evident on imaging studies. Ultimately, the patient is bedridden, unable to attend to even the simplest needs. After death, the brain can be analyzed for the disease's definitive neuropathology. Current criteria call for the presence of neuritic plaques and neurofibrillary tangles at specified densities (Figure 1).

The plaques are extracellular. They are best known for their content of A $\beta$ , a peptide of 40 or 42 amino acids that cells cleave from a larger molecule, the amyloid precursor protein (APP). The A $\beta$  monomers aggregate, forming fibrils that interact with stains such as Congo red. In this way, the lesions exhibit their defining amyloid appearance. However, the plaques also incorporate APP itself, as well as several other substances, including amyloid P, immunoglobulin G, complement proteins, the anticomplement protein clusterin, glycosaminoglycans, the glial protein  $\alpha$ 1-antichymotrypsin, and apoE. In all, more than 30 proteins have now been identified. After death, some patients with clinically probable Alzheimer's disease prove to have lacked sufficient plaques for a definitive diagnosis. Indeed, the neuropathologic criterion for neurofibrillary tangles is sometimes met despite an absence of plaques. Conversely, the brains of nondemented persons have sometimes been found to have enough plaques to support a definitive diagnosis.

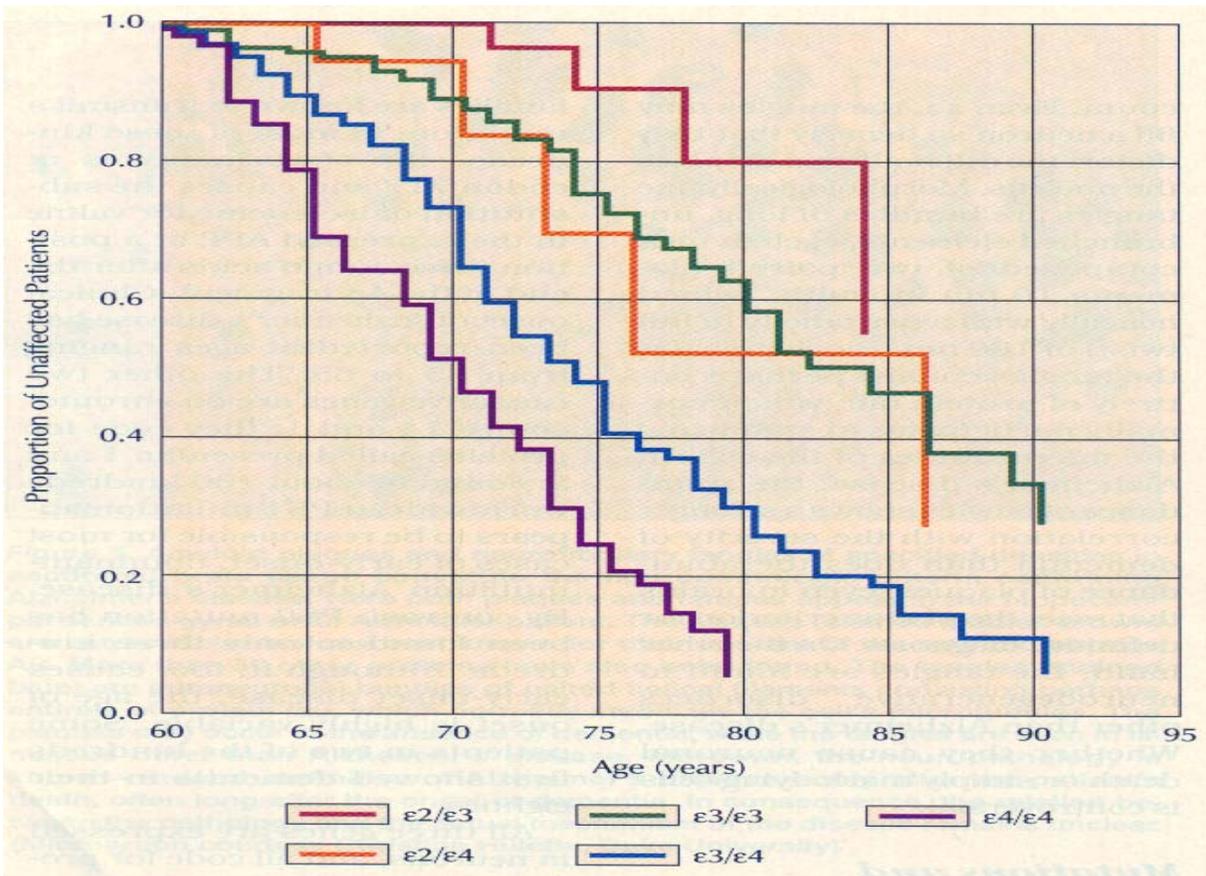
The tangles are intraneuronal. Hence, they can be observed post mortem only in neurons surviving until the patient's death, a fact that places a ceiling on their count. Even so, the tangles may fill a neuron so densely that they distort the cell body and displace the nucleus.

Morphologically, the tangles are bundles of long, un-branched elements, each in turn composed of two paired filaments 10 nm in width, twined helically with a periodicity (a full twist) of 160 nm. Biochemically, the tangles consist perhaps entirely of protein tau, which normally participates in stabilizing the microtubules of the cell. In Alzheimer's disease, the abundance of tangles shows a stronger correlation with the severity of dementia than does the abundance of plaques, even in brains that meet the plaque criterion for definitive diagnosis. On the other hand, the tangles are found in neurodegenerative disorders other than Alzheimer's disease. Whether they cause neuronal death or simply mark dying cells is controversial.

### ***Mutations and Polymorphisms***

Overall, the relation between the end-stage pathology of Alzheimer's disease and the actual mechanism responsible for cognitive impairment remains unknown. Elucidation of the function of genes implicated in the Alzheimer phenotype thus takes on special importance.

Of the three genes considered deterministic, the first to be discovered was the APP gene, on chromosome 21. Fewer than 20 families are known to transmit a mutation; in most of these kindreds, the abnormality is at codon 717 and causes the substitution of isoleucine for valine in the expressed APP, at a position three amino acids after the end of the A $\beta$  fragment. Clinical onset of Alzheimer's disease has been reported at ages ranging from 35 to 65. The other two causative genes are on chromosomes 14 and 1; they code for proteins called presenilin 1 and 2. Found in about 100 kindreds worldwide, a PS1 mutation appears to be responsible for most cases of early-onset, dominant-mutation Alzheimer's disease. By contrast, PS2 mutation has been found in only three kindreds. Although it, too, causes early-onset disease, the age of onset is highly variable. Some patients in two of the kindreds first showed dementia in their



**Figure 2.** Status of *APOE* genotype as a risk factor for late-onset, or sporadic, Alzheimer's disease is shown by data charting, for five genotypes, the age-related chance of staying free of the disease, as derived from 705 persons 60 or older at onset of symptoms or when examined and found to be normal. For  $\epsilon 4$  homozygotes, the median onset was before age 70, and by age 75, the chance of being unaffected was near 20%. For  $\epsilon 2/\epsilon 3$  heterozygotes, the median onset was after age 90. But since the gene does not cause the disease, the data cannot support predictions for individuals with unimpaired cognition. The *APOE* gene codes for apolipoprotein E, a lipid carrier known only for its relevance to cardiovascular disease when its involvement in neurodegenerative illness was identified in 1992.

eighties. All three genes are expressed in neurons, and all code for proteins inserted into cell membrane (though not necessarily at the cell surface). The proteins' functions remain elusive.

It has, however, been found that the longer of  $A\beta$ 's two major forms aggregates more readily than the shorter. Accordingly, proponents of the belief that amyloid deposition causes Alzheimer's disease suspect that the longer form is an especially potent killer of neurons. In patients with presenilin mutations, plasma concentrations of the longer form are reported to be twice those in normal persons. Moreover, in cultured cells, a mutated presenilin gene causes an increase in the longer form. The findings are sometimes offered as confirmation that  $A\beta$  causes Alzheimer's disease. But in the

common, late-onset form of Alzheimer's disease, the longer form does not show a similar predominance.

The susceptibility gene *APOE* is on chromosome 19. Of its three alleles, the most common,  $\epsilon 3$ , represents 78% of all alleles, while  $\epsilon 4$  accounts for 15% and  $\epsilon 2$  for 7%. The figures vary in different ethnic groups, especially with regard to  $\epsilon 2$  and  $\epsilon 4$ . Pairings of the alleles give six possible genotypes, of which  $\epsilon 3/\epsilon 3$  is the most common, found in some 60% of the U.S. population. In sporadic Alzheimer's disease, the median age of onset varies from less than 70 years for  $\epsilon 4$  homozygotes (about 2% of the U.S. population) to more than 90 years for  $\epsilon 2/\epsilon 3$  heterozygotes (about 10%). Persons homozygous for  $\epsilon 2$  are less than 0.05% of the population--too scarce for the distribution of age

of onset to have been analyzed. Still, from the available data, *APOE* genotype can be seen to create a difference of more than two decades in the timing of disease expression (Figure 2). It is likewise a factor in the expression of the disease in APP mutation kindreds. For instance, three persons in three different APP-mutation families are known to have the codon 717 mutation, but at an age more than two standard deviations beyond their families' mean age of onset they still show no signs or symptoms. In all three, the *APOE* genotype is  $\epsilon 2/\epsilon 3$ .

The epidemiology of *APOE* in relation to Alzheimer's disease can be expressed as a dose effect of  $\epsilon 4$ , with each copy increasing the risk of disease and shifting its onset to lower ages. About 30% of the population has at least one  $\epsilon 4$  allele. Conversely, each  $\epsilon 2$  allele decreases risk and increases mean age of onset. More than 15% of the population has at least one  $\epsilon 2$  allele. Extrapolation of the trends suggests that even if  $\epsilon 2/\epsilon 3$  were a universal inheritance, everyone would manifest Alzheimer's disease by age 140. In this perspective, Alzheimer's disease is the eventual outcome of a universal metabolic process, and the exiting distribution of *APOE* alleles simply enables it to appear early and often enough to be a prominent public health threat.

### *ApoE in the Brain*

At first glance, the susceptibility gene *APOE* might seem not quite as mysterious as the deterministic genes. At the time its status as a risk factor for sporadic Alzheimer's disease was first identified, in 1992, the gene and its product were well known from at least two decades of cardiovascular research.

The gene has four exons totaling 3,597 nucleotides; it codes for a 1,163-nucleotide messenger RNA, which in turn specifies apoE, with its 299 amino acids. The protein's chief source is the liver, but almost every tissue expresses it to some degree, including even muscle, albeit at low levels. Structurally, the protein has two hooks: a lipid-binding site, near its carboxy end, and a receptor-binding site, toward the amino end. These make apoE ca-

pable of carrying lipid in a soluble form in the blood and of delivering it to cells with the proper receptor. Among receptors, the classic one is the LDL receptor, but three others appear to exist in appreciable quantity. These are the LRP (LDL-related protein) receptor, the VLDL receptor, and glycoprotein 330, found mainly on kidney cells. At the targeted cell, apoE, its lipid cargo, and the receptor to which it binds are internalized by endocytosis. In the resulting endosome/lysosome, the lipid is detached in a pH-dependent process.

But what apoE does for peripheral organs may not be what it does in the brain. For one thing, peripheral apoE is denied entrance into the brain. If the liver of a donor with, say, an  $\epsilon 3/\epsilon 4$  genotype is transplanted into an  $\epsilon 3/\epsilon 3$  homozygote, the recipient's cerebrospinal fluid will show none of the  $\epsilon 4$  protein. The blood-brain barrier does not let apoE through. Instead, the brain relies exclusively on its own biosynthesis. As a maker of apoE, the brain is second only to liver.

Within rodent brain tissue, in situ hybridization studies have identified apoE mRNA exclusively in astrocytes and microglia. By contrast, recent immunohistochemical studies in humans and other primates have found it not only in glia but also in neurons. The mechanism responsible for its presence in the latter is not yet understood. If it were processed in the same way identified in the periphery, it--and presumably its cargo--would bind to LRP receptors, which neurons are known to express. After internalization by endocytosis, it would remain attached to cell membrane, which, however, would form a vesicular structure. Here, its cargo would be offloaded and the apoE itself would be degraded, or perhaps returned to the cell surface for release to extracellular space. ApoE would occur intraneuronally only in vesicles. Yet we have found it not only there but also in the



**Figure 3.** The genetic locus needed for expression of apoE in human neurons appears to include not only the *APOE* gene but also a control region situated some 18 kilobases downstream from the start of *APOE*, a distance that places the control region past a gene coding for apolipoprotein C1. The drawing shows a 30-kilobase span from the long arm of human chromosome 19 sufficient to induce expression of human apoE in mouse neurons.

neuronal cytoplasm. Conceivably, it leaked from endosomes. Alternatively, the LRP found on the neuronal surface might permit direct entrance.

A third possibility is that the neuron conducts a small amount of apoE biosynthesis, undetected derives from knockout mice lacking their own genes for apoE. In the absence of any further manipulation, the mice show the expected hypercholesterolemia--about 750 mg/dL, or five to six times normal--along with accelerated atherosclerosis. The insertion of human *APOE* tends to correct this peripheral defect. (In particular,  $\epsilon 3$  or  $\epsilon 4$  is corrective, but  $\epsilon 2$  is not, just as in humans.) Since 1993, however, it has been known that high-expression control of human *APOE* in mouse liver requires a region 18 kilo-bases downstream from the gene's promoter, a distance that places it after chromosome 19's next gene, which codes for apolipoprotein C1, and in an interval between *APOC1* and an *APOC* pseudogene (Figure 3).

In the mouse's brain, the findings are similar--and, in their way, dramatic. Among researchers, the wild-type mouse has been notorious for brain expression of apoE only in glia, not in neurons.

The negative finding has been a basis for dismissing hypotheses about Alzheimer's disease

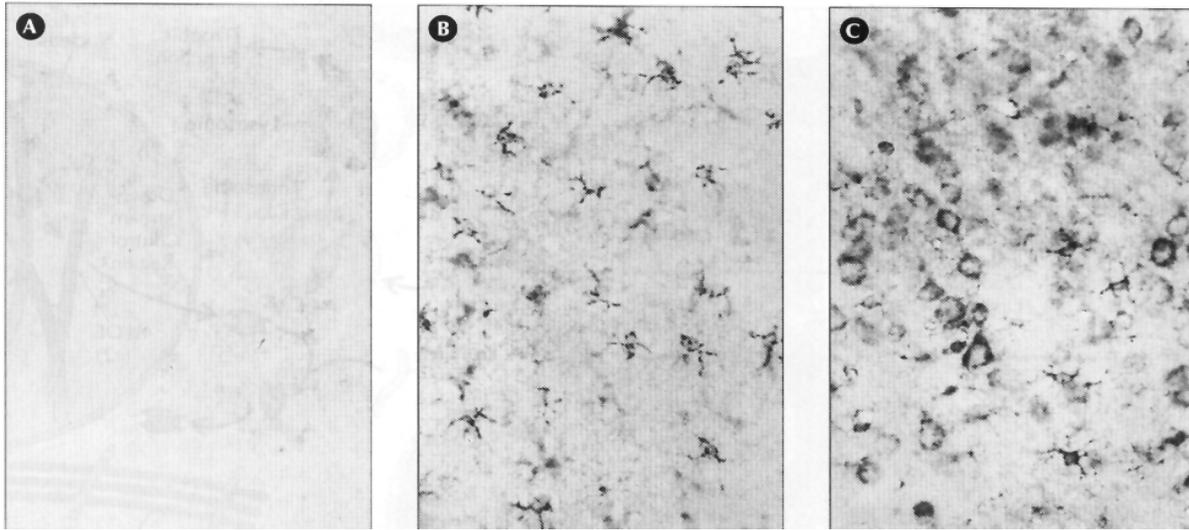
involving interaction between apoE and protein tau, the microtubule-associated protein that forms neurofibrillary tangles, on the grounds that apoE is outside a neuron while tau is inside. But when apoE knockout mice receive a human DNA span of about 30 kb, beginning 5 kb upstream from *APOE* and ending just past the

*APOC* pseudogene, human apoE mRNA becomes detectable Intraneuronally (Figure 4), with a distribution resembling that found in human studies. Evidently, in humans the regulatory element responsible for *APOE* ex

pression in hepatocytes may also govern its intraneuronal expression. The latter, however, is at a low level. Our experiments detect it most easily in animals given eight copies of the human DNA span, but it can be observed in two-copy animals as well.

In sum, astrocytes are the cells chiefly responsible for the human brain's prominence as a producer of apoE, but some human neurons appear to express it, too. For efforts to understand the pathogenesis of Alzheimer's disease, the implication is that apoE may interact with protein tau within the neuronal cytoplasm. For medical genetics, the implications are more

widespread. In a typical transgenic experiment, a span of human DNA matching only the exons of a disease-related gene is joined to a promoter selected for its robustness in inducing gene expression. The intent is to discover whether an animal given this construct will express at least facets of the disease phenotype. Often, the animal shows no disease. Our findings confirm that a gene's cellular expression pattern can be governed by DNA sequences far outside the gene itself. Such governance (or misgovernance) might be crucial for the gene product's



**Figure 4.** Genetic manipulations of *APOE* in the mouse create dramatic alterations in brain expression of apoE. Lacking both copies of its own *APOE* gene, a young adult knockout mouse shows no apoE protein (A). In particular, immunostaining of the animal's cerebral cortex with anti-rodent apoE yields only faint background labeling with no discernible cellular elements. In a wild-type mouse, some cells do stain, but they are exclusively glia--notably, spidery looking astrocytes (B). In a knockout mouse given two copies of human *APOE*  $\epsilon 3$ , along with surrounding DNA (as in Figure 3), glia labeled by anti-human apoE are joined by clearcut staining of neurons (C). Somehow, too, they affect how well the brain responds to insult. In a consecutive series of patients hospitalized for spontaneous intracerebral hemorrhage, the 30-day death rate was 70% for  $\epsilon 3/\epsilon 4$  patients, compared with 30% for  $\epsilon 3/\epsilon 3$  homozygotes. Likewise, neuropsychological testing before and six weeks after elective cardiac bypass surgery showed a small but significantly greater postoperative deficit among  $\epsilon 4$  carriers.

involvement in disease pathogenesis, but standard techniques would fail to reveal it.

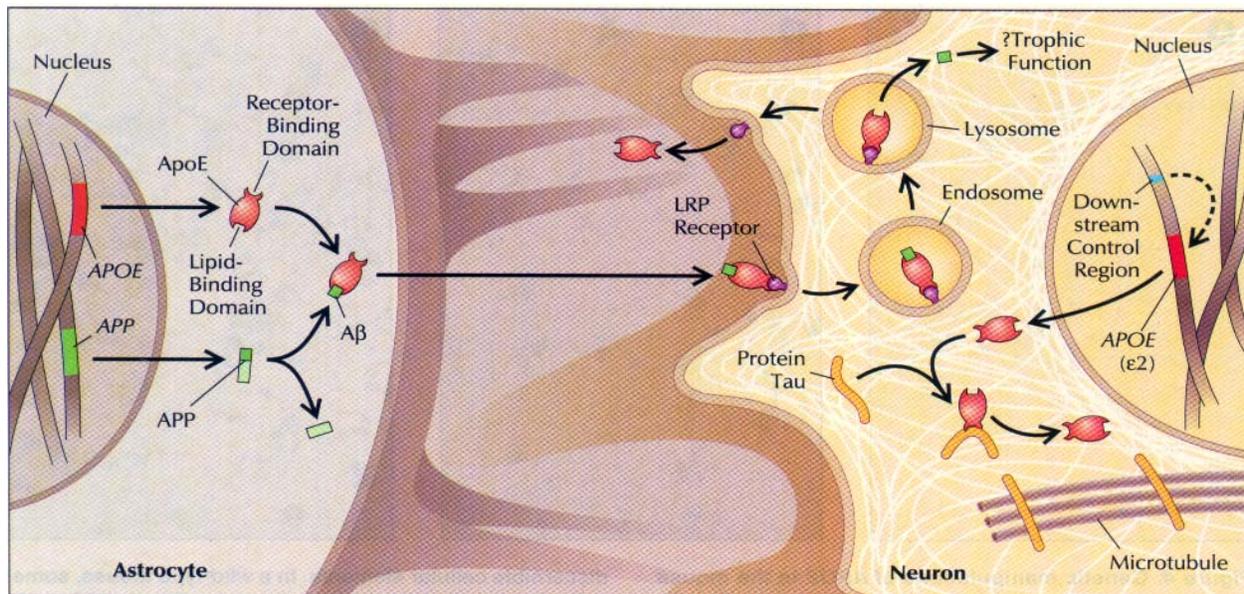
### ***Isoform-Specific Metabolism***

How then does *APOE* genotype affect the risk of Alzheimer's disease? In biomolecular terms, the allele types must differentially influence the rate of a lifelong metabolic process. In primary structure, the proteins specified by the alleles of *APOE* are much alike. Indeed, the sole differences involve cysteines at two sites. Among its 299 amino acids, apoE3 has cysteine only at position 112. ApoE2 has an additional cysteine at position 158 (where E3 has arginine). ApoE4 has no cysteines. (Instead, positions 112 and 158 both show arginine.) Nevertheless, the isoforms differ markedly both in their binding of lipids and in their interaction with receptors. Among lipids, the E2 and E3 isoforms preferentially bind HDL, whereas E4 shows strongest affinity for the triglyceride-rich LDL particles, including VLDL. Among receptors, E3 and E4 bind the LDL receptor

with high affinity, whereas E2 binds with only about 1% the affinity of E3.

The isoforms also differ in properties perhaps more pertinent to Alzheimer's disease. In vitro, apoE binds to protein tau. For the E3 isoform, the binding is stronger and more enduring than it is for E4. On the apoE side, the interaction involves the site classically used for binding to a receptor. On the tau side, the interaction involves the site required for receptor binding as well as binding to  $\beta$ -tubulin, a constituent of microtubules. It is also the site at which two taus can bind to each other, creating the twined homodimers called paired helical filaments. After the homodimerization, tau is incapable of binding to either E3 or E4. However, the homodimers can aggregate into neurofibrillary tangles.

The findings suggest the hypothesis that in



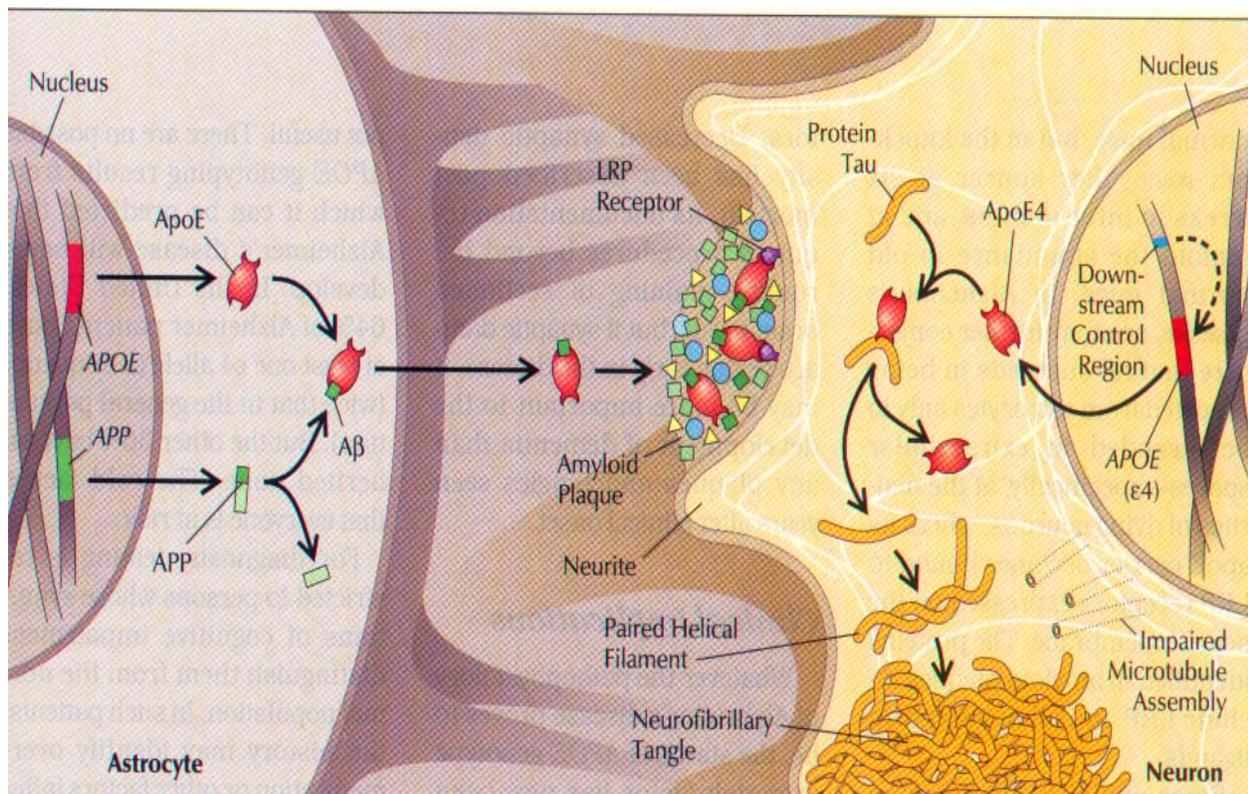
**Figure 5.** Functions of apoE in the brain remain highly speculative but may be quite different than in the liver or blood vessels. In the human brain the protein is expressed chiefly in astrocytes (left), which also produce amyloid precursor protein (APP), from which the amyloid peptide Aβ is cleaved. Conceivably, apoE conveys Aβ to brain neurons (right), where binding to LDL-related protein (LRP) might permit its internalization for a trophic function as yet unknown. For its part, the apoE might be recycled. Within the neuron, the control region downstream from APOE permits low-level expression of apoE. In the neuronal cytoplasm, apoE's presence may protect a binding site on protein tau, keeping the protein available to form stabilizing cross-bridges on microtubules. In vitro, the affinities of apoE for Aβ (at apoE's Lipid-binding site) and protein tau (at apoE's receptor-binding site) depend on the apoE isoform. The one depicted is apoE2, as coded by the ε2 allele of APOE.

the neuronal cytoplasm, E3 protects tau's microtubule-binding site, keeping tau available for interaction with β-tubulin (Figure 5). When the tau/apoE complex arrives at a microtubule, the apoE is displaced, freeing tau for its normal function. In the current view, the protein forms stabilizing cross-bridges among microtubule assemblies. ApoE4 lacks the site-protective capacity of E3. Accordingly, in dose-related fashion, E4 gives tau a more prolonged opportunity to homodimerize. Hence, on a time scale measured in years, microtubule maintenance, remodeling, and repair would become progressively less efficient.

Suppose some injury occurs. Microtubules, the thickest of a neuron's cytoskeletal elements, can reassemble to change an internal scaffold that maintains the neuron's shape and synaptic integrity; they also serve as tracks for the rapid transport of molecules, and even organelles, along an axon or dendrite. Thus there is reason to think that microtubules are essential for the

ability of a neuron to respond to stress—including the stress of living. If apoE4 creates a slow bias toward tau homodimerization, impairing microtubule homeostasis (Figure 6), neurons may fail more rapidly, in a process marked clinically by dementia and neuropathologically by brain atrophy and neurofibrillary tangles.

In vitro, apoE also interacts with Aβ. In this case, the E4 isoform binds more avidly than E3. The binding appears to depend on an oxidative change in apoE, which may be speedier in E4. Binding is at the site apoE classically uses to carry a lipid. In fact, Aβ is hydrophobic, and in that sense lipidlike. After several days of in vitro incubation, apoE and Aβ form fibrils, E4 more so than E3. The findings suggest that in the



**Figure 6.** In theory, apoE may affect metabolic processes leading to Alzheimer's disease as follows: ApoE may exit astrocytes carrying a cargo of Aβ only to get trapped by LRP on the surface of the neurites of dying neurons. (The plaques of Alzheimer's disease incorporate LRP and all of its known ligands, including apoE.) Within the neuron, escape of protein tau from protective binding to apoE may enable it to homodimerize, creating paired helical filaments that in turn form neurofibrillary tangles. In the absence of protein tau, microtubules cannot assemble—a process that is essential to the cell's shape and synaptic integrity. The apoE isoform depicted is apoE4, as coded by the E4 allele of *APOE*, each copy of which increases the risk of Alzheimer's disease and shifts the onset to younger ages. Among the three apoE isoforms, E4 shows the highest affinity for NS and the lowest for protein tau.

brain, the apoE synthesized abundantly in astrocytes might serve as the carrier of astrocytic Aβ, solubilizing the latter for passage to neurons, where it might have a trophic function as yet unknown. Since Aβ binds to apoE's hook for a lipid, the other hook presumably remains free to interact with a neuron's LRP receptor. The ensuing internalization might direct Aβ to endosome/lysosomes for pH-dependent dissociation.

If this conjecture is valid, apoE knockout should leave Aβ stranded in astrocytes, where it would aggregate. In fact, in knockout mice we have now found it there by three techniques: electron microscopy, Congo red staining, and immunoreactivity. At about 18 months, the aggregations are detectable in the astrocytes of normal mice, but in the knockout mice, they

appear at six weeks to three months, and at tenfold the abundance in old normal mice. In Alzheimer's disease, one may further conjecture that Aβ succeeds in being exported from astrocytes only to be stranded in extracellular spaces—specifically, at the neurites of dying neurons, where its apoE carrier becomes bound to LRP receptors expressed on the neurite membrane. The proteins identified in amyloid plaques include LRP and all of its known ligands.

Since apoE4 holds Aβ more avidly than E3 does, the conjecture accounts for observations that for equal duration of Alzheimer's disease (as measured from time of diagnosis), the brains of patients homozygous for e4 show more extensive extracellular amyloid deposition, in

larger, denser, more congophilic plaques, than the brains of patients homozygous for  $\epsilon 3$ . Even so, the duration of disease (measured from diagnosis to death) is no different in the two groups. On this basis, the clinical course of the disease is independent of amyloid deposition. Indeed, it is now generally accepted that the dementia of Alzheimer's disease correlates better with intraneuronal tangles than with extraneuronal plaques.

Still, some investigators have begun to suspect that neither the plaques nor the tangles constitute the disease's primary effectors. Decreased synaptic density has been described post mortem. Its documentation requires procedures beyond the routine staining of sectioned brain tissue, but if synaptic damage begins early in the disease, it may be more important to the development of dementia than any plaques and tangles seen years after clinical onset.

### ***Clinical Implications***

Whatever the pathophysiology of Alzheimer's disease proves to be, the status of *APOE* genotype as a risk factor has now been confirmed in more than 150 studies worldwide. To me, the clinical implications seem fundamentally simple--for now. They emerge from the recognition that the *APOE* alleles are susceptibility polymorphisms, not mutations. They neither cause nor prevent the disease. In consequence, among persons showing no sign of cognitive impairment, the positive predictive value of *APOE* genotype is insignificant: A subject's wish for foreknowledge goes unanswered, except for the unsatisfactory information that some genotypes carry increased relative risk. The group with the highest risk is the 2% of the population with an  $\epsilon 4/\epsilon 4$  genotype, but even for them, the risk spans five decades from age 50 through the 90s, and some will never get the disease. The negative predictive value is likewise not useful. There are no possible *APOE* genotyping results from which it can be predicted that Alzheimer's disease will never develop. In the United States, 64% of Alzheimer patients have at least one  $\epsilon 4$

allele (a frequency twice that in the general population). But the other 36% have inherited none. The cold fact is that everyone is at risk.

For diagnosis, testing is restricted to persons whose symptoms of cognitive impairment distinguish them from the normal population. In such patients, the history may identify over-medication or other factors influencing cognition. Laboratory tests may disclose electrolyte imbalance, hyperthyroidism, or, less often, vitamin B12 deficiency presenting as dementia. Neurologic findings may direct suspicion toward tumor or stroke. In some instances, a patient's behavior may suggest an etiology such as Wernicke's encephalopathy. When all such avenues have been explored, what remains is a clinical impression of possible Alzheimer's disease. The cognitive impairment is consistent with the disease, there appears to be no reversible cause, and the neurologic examination's findings are nonfocal.

In groups of such persons, the positive predictive value of *APOE* genotype can be measured empirically. At the Duke Memory Disorders Clinic, my colleagues and I identified all patients who had been followed from an initial diagnosis of possible Alzheimer's disease until the patient's eventual death in the probable-Alzheimer category. In all 67 cases, an autopsy was performed. Like virtually every other specialty clinic, we were about 85% correct. The rest of the cases failed to meet the neuropathologic criteria for definitive diagnosis. In brain samples preserved by paraffin block, we then determined *APOE* genotype. For the 43 that had one or two  $\epsilon 4$  alleles, the positive predictive value of *APOE* genotyping was 100%. In other words, every patient with a clinical diagnosis of probable Alzheimer's disease and an  $\epsilon 4$  allele indeed had Alzheimer's disease.

At the Royal Perth Hospital in Australia, the neuropathologist Byron A. Kakulas performed a similar analysis for a somewhat broader group, consisting of all patients who had been referred with the word "dementia" or Alzheimer's" in the referral document, and who had died and been autopsied within the preceding 10 years. Not surprisingly, a substantial proportion did not

have Alzheimer's disease. Nevertheless, the positive predictive value of an  $\epsilon 4$  allele was 100%.

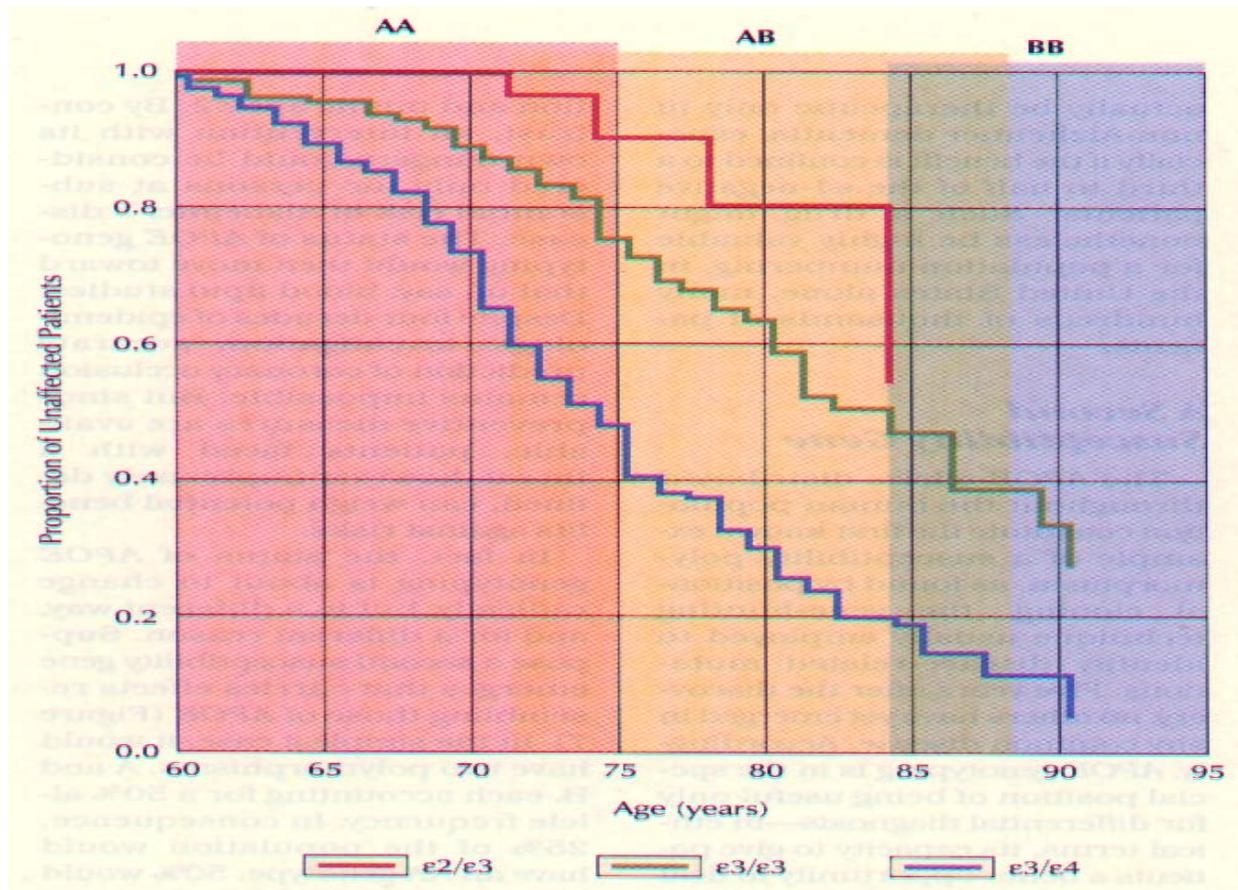
Finally, we analyzed cases from the CERAD project. CERAD--the Consortium to Establish a Registry for Alzheimer's Disease--is a collaboration among more than 20 American centers. Recruited patients agree to be followed and to eventual autopsy. Among studies published since 1988, initial reports have described neuroimaging and neuropsychological attributes of the disease, and subsequent ones have addressed neuropathologic findings. Again, about 85% of clinical diagnoses have been correct. Our center undertook blind *APOE* genotyping of the CERAD autopsy series. Of about 200 autopsies, brain tissue in 162 had been preserved in a suitable form. Of these, 119 showed an  $\epsilon 4$  allele. The positive predictive value for definite Alzheimer's disease was 97%. In four instances, an autopsied  $\epsilon 4$ -positive case did not receive a primary diagnosis of Alzheimer's disease. In two, however, the secondary diagnosis was definite Alzheimer's disease. Including them would make the positive predictive value 98%. In the remaining two, the pathologist's findings had included "possible Alzheimer's disease."

How then should *APOE* genotyping be used? If patients with symptoms of dementia, no reversible cause, and a nonfocal neurologic examination are simply said to have Alzheimer's disease, 55% to 65% of these diagnoses will be correct. (Alzheimer's disease accounts for that proportion of dementia.) If the disorder progresses to probable Alzheimer's disease and the patient is followed until death, the diagnostic accuracy will be 85%. But if *APOE* genotyping performed early in the disease identifies an  $\epsilon 4$  allele, the accuracy rises immediately to at least 97%-- positive predictive value that calls into question the cost-effectiveness of multiple brain imaging studies, which are commonly performed. In the wake of an  $\epsilon 4$  finding, the patient's age can give an estimate of how long the disease is likely to last. Moreover, if the finding becomes known sufficiently early, while cognitive function and memory are largely intact, the patient can participate in planning his

or her care, and in deciding how to spend the time remaining.

In brief, a positive test provides information to be used like any other prognostic information pertaining to a life-threatening illness. If the test is negative--the patient has no  $\epsilon 4$  alleles--the likelihood that the disorder is Alzheimer's disease still exceeds 50%. However, entities that can be confused with Alzheimer's disease will tend to be concentrated within this group. Hence, negative results identify cases in which expenditure of diagnostic resources will have the greatest yield.

For testing of possible therapies of Alzheimer's disease, *APOE* genotyping may likewise be important. However, its use requires interpretive caution, as suggested by events surrounding the testing of tacrine. The drug--the first to be approved as specific Alzheimer therapy, is an acetylcholinesterase inhibitor. The impetus for its development was the finding, from the mid-1970s, of acetylcholine deficiency in the cortex of Alzheimer patients. When the status of *APOE* genotype as a risk factor for Alzheimer's disease became known, genotyping became a part of the clinical trials. In one such effort, involving only 40 patients, the drug's 30-week benefit was found to correlate with absence of  $\epsilon 4$ . Hence, the allele was taken to predict a poor therapeutic response. But since apoE4-negative patient group includes a substantial proportion in whom the impression of Alzheimer's disease is mistaken, the findings can also be interpreted as suggesting that the drug is effective only in patients *without* Alzheimer's disease. Tacrine has now been joined by donepezil, an agent with less hepatotoxicity and a more convenient dosing schedule. In general, a drug effective against Alzheimer's disease ought to show benefit in E4-positive patients. Indeed, a drug effective



**Figure 7.** Discovery of a second gene conferring allele-related susceptibility to Alzheimer's disease might make prediction almost as accurate as current tests for a mendelian illness. The illustration superimposes on the known risk pertaining to three APOE genotype the age-of-onset distributions attached to a second, hypothetical susceptibility gene whose allele A and B create the genotypes AA, AB, and BB. Allele A, like the E4 allele of APOE, exerts a dose-related adverse effect. By itself, APOE genotyping cannot predict Alzheimer's disease. But perhaps among E3/E4 heterozygote, those at high risk within a typical human lifespan carry the second gene's allele A. A second susceptibility gene for Alzheimer's disease will be identified within the next year or two.

specifically against Alzheimer's disease should be most consistently beneficial in an E4-positive group, with its few non-Alzheimer patients.

Thus, for testing of possible therapies, the true benefit of APOE genotyping lies in its ability to select, among patients with cognitive impairment, a group nearly homogeneous for Alzheimer's disease. Conversely, a drug beneficial exclusively in a non- $\epsilon 4$  group may actually be therapeutic only in non-Alzheimer dementia, especially if the benefit is confined to a third to half of the  $\epsilon 4$ -negative patients. Such a drug might nonetheless be highly valuable for a population numbering, in the United States alone, many hundreds of thousands of patients.

### *A Second Susceptibility Gene*

The APOE alleles distributed throughout the human population constitute the first known example of a susceptibility polymorphism, as found by positional cloning, the gene-hunting technique usually employed to identify disease-related mutations. Accordingly, APOE genotyping is in the special position of being useful only for differential diagnosis---in ethical terms, its capacity to give patients a better opportunity to deal with Alzheimer's disease. (The test is licensed by Duke University exclusively to Athena Neurosciences, which requires a physi-

cian's signature attesting that the patient is cognitively impaired.)

If a preventive treatment were found, the role of the testing might change. An innocuous intervention could simply be used by everyone, such as vitamin C for preventing scurvy. The treatment might be designed to enter neurons at very low concentration and mimic apoE2. By contrast, an intervention with its own dangers could be considered only for persons at sub- Accordingly, APOE genotyping is in the special position of being useful only for differential diagnosis---in ethical terms, its capacity to give patients a better opportunity to deal with Alzheimer's disease. (The test is licensed by Duke University exclusively to Athena Neurosciences, which requires a physician's signature attesting that the patient is cognitively impaired.)

If a preventive treatment were found, the role of the testing might change. An innocuous intervention could simply be used by everyone, such as vitamin C for preventing scurvy. The treatment might be designed to enter neurons at very low concentration and mimic apoE2. By contrast, an intervention with its own dangers could be considered only for persons at substantial risk of Alzheimer's disease. The status of *APOE* genotyping would then move toward that of, say, blood lipid studies. Despite four decades of epidemiologic investigation, accurate prediction of coronary occlusion remains impossible. But since preventive measures are available, patients faced with a threat, however imprecisely defined, can weigh potential benefits against risks.

In fact, the status of *APOE* genotyping is about to change radically, but in a different way, and for a different reason. Suppose a second susceptibility gene emerges that carries effects resembling those of *APOE* (Figure 7). In the simplest case, it would have two polymorphisms, A and B, each accounting for a 50% allele frequency. In consequence, 25% of the population would have an AA genotype, 50% would have AB, and 25% BB. Suppose each A is unfortunate, increasing the likelihood of Alzheimer's disease and decreasing its age of onset, whereas B does the reverse. The risks

must be superimposed on those for *APOE* genotype. Thus, an  $\epsilon 3/\epsilon 4$  *APOE* heterozygote cannot currently be told when, or even whether, Alzheimer's disease will occur. But if testing for the second susceptibility gene disclosed AA, the disease might be highly likely before age 70. Conversely, a person with an  $\epsilon 3/\epsilon 4$  BB inheritance might have little reason to fear the disease.

In sum, a second susceptibility gene could have the unsettling effect of making prediction of Alzheimer's disease almost as accurate as a test for a mutated gene, or perhaps of making the predicted age range of onset even more accurate. The second gene will be identified within a year or two. It has already been traced to a location on chromosome 12, and candidate genes in the region have been identified. The groups at risk will not be small. For example, the  $\epsilon 3/\epsilon 4$  *APOE* genotype accounts for 20% of the U.S. population. By the foregoing hypothetical statistics, AA will occur in a fourth of that group. The medical community has no experience with an ability to predict illness on such a scale. Still, disorders including osteoarthritis, diabetes mellitus, atherosclerosis, and asthma will eventually reveal their own susceptibility genes. Thus, the dilemmas of testing for risk of Alzheimer's disease--the current situation, and the problems soon to arise---are sure to recur in many other diseases. □

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## Alzheimer's Disease

# MUTANT GENES IN FAMILIAL ALZHEIMER'S DISEASE AND TRANSGENIC MODELS

*Donald L. Price and Sangram S. Sisodia*

Departments of Pathology (DLP, SSS), Neurology (DLP), Neuroscience (DLP, SSS), and the Division of Neuropathology (DLP, SSS), The Johns Hopkins University School of Medicine, Baltimore, Maryland 21205-2196; e-mail: ADRC@welchlink.welch.jhu.edu, ssisodia@welchlink.welch.jhu.edu

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## ABSTRACT

The most common cause of dementia occurring in mid- to late-life is Alzheimer's disease (AD). Some cases of AD, particularly those of early onset, are familial and inherited as autosomal dominant disorders linked to the presence of mutant genes that encode the amyloid precursor protein (APP) or the presenilins (PS1 or PS2). These mutant gene products cause dysfunction/death of vulnerable populations of nerve cells important in memory, higher cognitive processes, and behavior. AD affects 7-10% of individuals >65 years of age and perhaps 40% of individuals >80 years of age. For the late-onset cases, the principal risk factors are age and apolipoprotein (apoE) allele type, with apoE4 allele being a susceptibility factor. In this review, we briefly discuss the clinical syndrome of AD and the neurobiology/neuropathology of the disease and then focus attention on mutant genes linked to autosomal dominant familial AD (FAD), the biology of the proteins encoded by these genes, and the recent exciting progress in investigations of genetically engineered animal models that express these mutant genes and develop some features of AD.

## INTRODUCTION

Age-related impairments in cognition and memory have been known since ancient times, but the clinical-pathological features of the syndrome, now termed Alzheimer's disease (AD), were not documented in the medical literature until the first decade of this century. It is now established that AD is the most common type of dementia occurring in mid- to late life, affecting 7-10% of individuals >65 years of age and perhaps 40% of persons >80 years of age (McKhann et al 1984, Evans et al 1989). The prevalence of this disease, which now affects >4 million individuals in the United States, is increasing because of very significant shifts in life expectancy and demographic parameters. In 1900, 1% of the world's population was >65 years of age; in 1992, that figure was 6.2%; in 2050, it is estimated that ~25% of the population will be >65 years of age (Olshansky et al 1993).

Some cases of AD are inherited autosomal dominant disorders linked to the presence of mutant genes that encode the amyloid precursor protein (APP) or the presenilins (PS 1 or PS2). These mutant gene products cause dysfunction/death of vulnerable populations of nerve cells, with the resulting clinical syndrome of progressive dementia. After a brief discussion of the clinical syndrome of AD and the neurobiology/neuropathology of disease, this review focuses on mutant genes linked to autosomal dominant familial AD (FAD), the biology of the proteins encoded by these genes, and investigations of genetically engineered animal models.

## CLINICAL FEATURES OF AD

In 1907, Alois Alzheimer (Alzheimer 1907a,b) reported the case of a middle-aged woman who developed memory deficits and progressive loss of cognitive abilities accompanied by morbid jealousy. Autopsy disclosed the now-recognized classic pathology of AD--neurofibrillary tangles and

senile plaques in the neocortex and hippocampus. The majority of patients with the sporadic disease exhibit clinical signs during the seventh decade, whereas individuals with inherited AD often become demented in midlife. Affected individuals show abnormalities of memory, problem solving, language, calculation, visu-spatial perceptions, judgment, and behavior (McKhann et al 1984); some cases show psychotic symptoms, such as hallucinations and delusions. Activities of daily living become increasingly impaired, and in late stages of the disease, patients are often mute, incontinent, and bedridden and usually die of intercurrent medical illnesses.

### NEUROBIOLOGY/NEUROPATHOLOGY OF AD

#### *Vulnerable Neural Systems*

AD selectively affects neurons in certain brain regions and neural systems, including nerve cells in the cortex, hippocampus, amygdala, anterior thalamus, basal forebrain, and several brain stem monoaminergic nuclei (Whitehouse et al 1982, Hyman et al 1984, De Souza et al 1986, Hyman et al 1990, Morris et al 1991, Braak & Braak 1994, Braak et al 1996, Gómez-Isla et al 1997). Abnormalities occur in large pyramidal neurons of neocortex (Mann et al 1988, Mesulam & Geula 1988, Gómez-Isla et al 1997); several populations of cortical interneurons (De Souza et al 1986); pyramidal neurons of the entorhinal cortex and hippocampus (Samuel et al 1994, West et al 1994, Gómez-Isla et al 1996); basal forebrain cholinergic neurons (Struble et al 1986); and several other populations of neurons, including nerve cells in the amygdala, anterior nucleus of the thalamus, raphe, and locus coeruleus.

#### *Cytoskeletal Abnormalities*

Many affected nerve cells exhibit intracellular accumulations of single straight filaments and paired helical filaments, which are the ultrastructural substrates of neurofibrillary tangles (in cell bodies), neurites (in distal axons/terminals), and neuropil threads (in dendrites) (Arnold et al 1991, Braak & Braak 1994). These poorly soluble abnormal filaments are comprised principally of phosphorylated tau, a low molecular weight microtubule-associated protein (Grundke-Iqbal et al 1986, Lee et al 1991). In vitro studies have shown that the exposure of non-phosphorylated three- and four-repeat recombinant tau to high concentrations of sulphated glycosaminoglycans can lead to the formation of paired helical filaments and single-stranded filaments, respectively (Goedert et al 1996). These findings question the significance of tau phosphorylation and suggest that interactions of tau and glycosaminoglycans may play an important role in the formation of abnormal filaments in vivo. Because phosphorylated tau binds microtubules poorly and alters their stability, modifications of tau could have effects on intracellular transport, cellular geometry, and neuronal viability; eventually, abnormal nerve cells die, possibly by apoptosis (Lassmann et al 1995, Smale et al 1995, Troncoso et al 1996).

#### *Neuritic Plaques*

Senile or neuritic plaques--which are abundant in the amygdala, hippocampus, and neocortex in cases of AD (McKhann et al 1984, Morris et al 1996)---are comprised of dystrophic neurites displayed in proximity to thioflavin S/Congo Red-positive deposits of  $\beta$ -amyloid protein ( $A\beta$ ), 39- to 42-amino acid peptides derived from APP (Glennet & Wong 1984). The deposition of  $A\beta$  42 in the neural parenchyma occurs early, and this peptide species predominates in mature plaques. At peptides are also evident in the walls of blood vessels (conophilic angiopathy) (Glennet & Wong 1984, Iwatsubo et al 1994, Lemere et al 1996b). These A fibrillar aggregates act as a nidus for subsequent deposits of other proteins, including  $\alpha$ -antichymotrypsin; components of the complement cascade, and apolipoproteins E and J (apoE, apoJ) (Rogers et al 1988, Snow et al 1988). Moreover, deposits of  $A\beta$  and other proteins may play a role in the recruitment of astrocytes and microglial cells that are often

## Mutant Genes in Familial Alzheimer's Disease

conspicuous around plaques. Significantly, A $\beta$ 42 appears to be toxic to nerve cells (Yankner 1996), but the mechanisms of AB fibrillogenesis/toxicity are not well understood (see below).

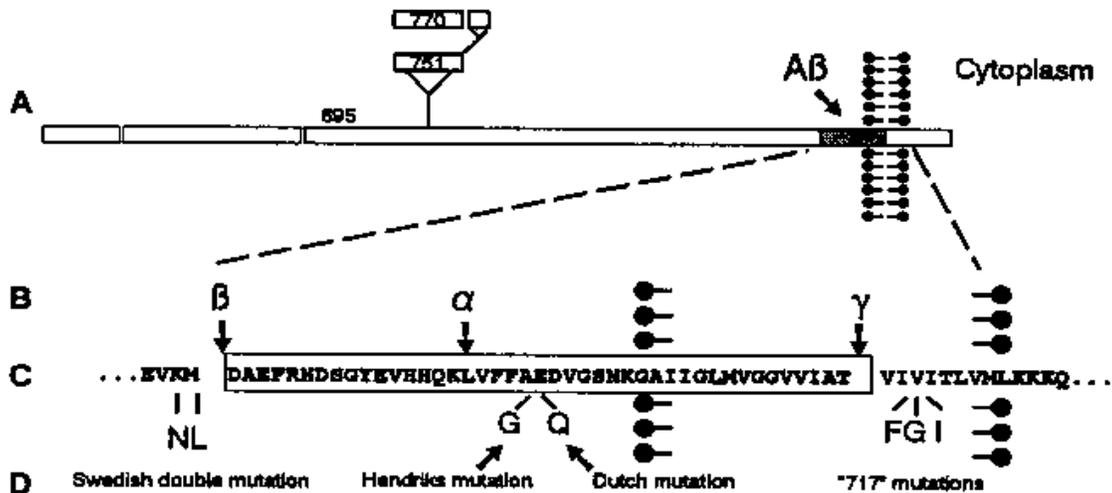
### *Evolution of Cellular Abnormalities and Relationship to Clinical Signs*

In a series of studies of the evolution of pathology, Braak & Braak (1994) identified six stages of AD that sequentially involve specific architectonic units. In stages I and II, lesions are present in the transentorhinal area and the CA fields of hippocampus. In stages III and IV, lesions appear in the hippocampus, basolateral amygdala, and limbic nuclei of the thalamus. In stages V and VI, cellular pathology involves the isocortex. The principal consequence of these lesions is a diminution of synaptic inputs in these regions of the brain (Masliah et al 1989, DeKosky & Scheft 1990, Terry et al 1991, Masliah et al 1992). Abnormalities that interrupt rostral temporal cortical and hippocampal circuits play central roles in memory impairments, whereas alterations in the basal forebrain cholinergic system may contribute to attentional and memory difficulties. Higher cognitive deficits--such as disturbances in language, praxis, and judgment--are related to pathology in the neocortex, whereas the psychiatric disturbances that occur in some patients may reflect involvement of the limbic cortex, amygdala, thalamus, and monoaminergic systems.

## GENETICS OF AUTOSOMAL DOMINANT FAD

To date, autosomal dominant FAD has been linked to the presence of mutations in three genes--APP, PS 1, and PS2. The risk of apoE allele type is a susceptibility locus with apoE4 showing dose-dependent contributions in cases of late-onset familial and sporadic AD (Roses 1995, 1996; Hyman 1996; Hyman et al 1996; Soininen & Riekkinen 1996).

Figure 1 Schematic representation of amyloid precursor protein (APP) and  $\beta$ -amyloid protein (A $\beta$ ). Proteolytic



cleavage sites required for APP  $\alpha$ -secretase (APP<sup>sa</sup>) secretion (a) and A $\beta$  production ( $\beta$ ,  $\gamma$ ) and the location of familial Alzheimer's disease (FAD)-linked mutations are shown. [Modified from Price et al (1996).]

APP

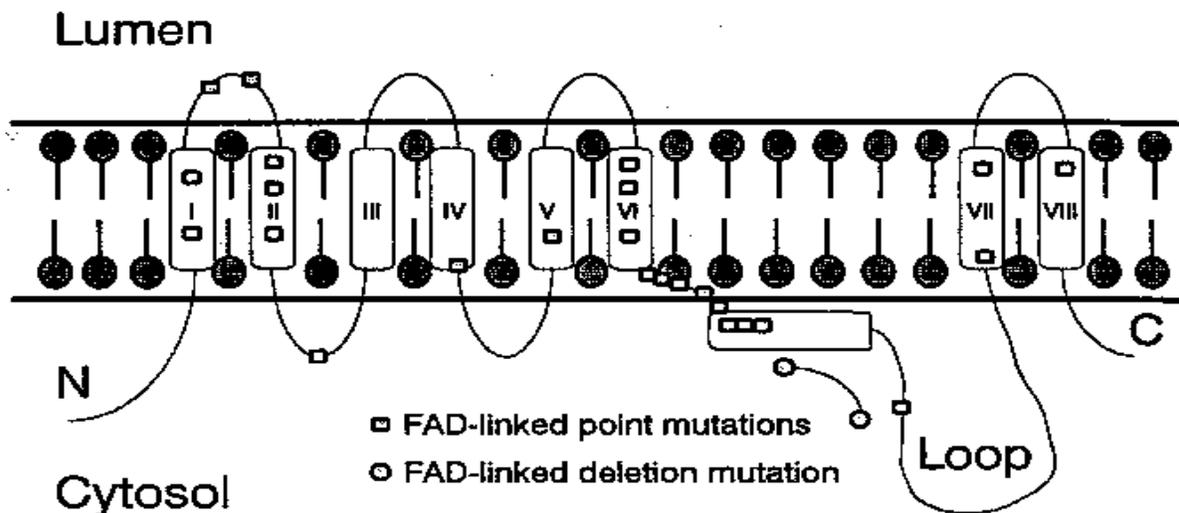
## Alzheimer's Disease

Encoded by a gene on chromosome 21, APP is a type-I integral membrane glycoprotein (Figure 1) containing the A/ $\beta$  region, comprised of 28 amino acids of the ectodomain and 11-14 amino acids of the adjacent transmembrane domain (Glenner & Wong 1984, Masters et al 1985). The first APP pathogenic mutation, a Glu-Gln substitution at codon 693 (of APP-770), was identified in a kindred with autosomal dominant hereditary cerebral hemorrhage with amyloid, Dutch type (HCHWA-D). This disease is manifested as adult-onset cerebrovascular disease, with death usually occurring by the sixth decade (Levy et al 1990, Van Broeckhoven et al 1990); in these individuals, A $\beta$  is deposited in the cerebral vessels. In ~ 12 early-onset pedigrees of FAD (Goate et al 1991, Mullan et al 1992), missense mutations have been demonstrated that lead to amino acid substitutions at residue 717 (of APP-770) within the transmembrane domain of APP (Chartier-Harlin et al 1991, Goate et al 1991, Naruse et al 1991). In two large related families from Sweden (Mullan et al 1992), early-onset AD has been linked to a double mutation at codons 670 and 671 that resulted in the substitution of Lys-Met to Asn-Leu. Finally, in one family with a Gly-Ala substitution mutation at codon 692 of APP, affected individuals developed presenile dementia, cerebral hemorrhages, diffuse deposits of A $\beta$ , congophilic angiopathy, and scattered senile plaques but no tangles (Van Broeckhoven et al 1990, Hendricks et al 1992).

The clinical, neuropathological; and genetic characteristics of APP-linked FAD in patients with APP mutations have several shared features, including onset before the age of 60 (mean family onset between 43 and 55 years), autosomal dominant inheritance fully penetrant by the early 60s, and clinical and pathological phenotypes indistinguishable from individuals with sporadic AD.

### Presenilins

Encoded by genes on chromosomes 14 and 1, PS1 and PS2, respectively, are highly homologous 43- to 50-kDa proteins (Levy-Lahad et al 1995a, b; Sherrington et al 1995) predicted to contain eight transmembrane helices (Doan et al 1996) (Figure 2). More than 30 missense mutations have been identified (Campion et al 1995, Cruts et al 1995, Sherrington et al 1995) in PS1, and these mutations



*Figure 2* Topology of presenilin 1 (PS 1). The membrane-spanning domains of PS 1 and the sites of several familial Alzheimer's disease (FAD)-linked mutations are shown. [Modified from Doan et al (1996).]

## Mutant Genes in Familial Alzheimer's Disease

account for up to 25-30% of early-onset cases of FAD. Many of these mutations occur within transmembrane domains or immediately adjacent to the predicted loop domain (Alzheimer's Disease Collaborative Group 1995, Sherrington et al 1995). A large family from Colombia has a Glu280-Ala mutation; affected individuals show massive deposits of AB42 in many brain regions (Lemere et al 1996b). In two families with early-onset FAD, an unusual point mutation has been identified upstream of a splice acceptor site, resulting in an in-frame deletion of exon 9 (amino acids 290-319) (PS 1 AE9) (Perez-Tur et al 1995). Two PS2 mutations have been reported to cause autosomal dominant AD in Volga German kindreds (with onset at 50-64 years of age) and in an Italian pedigree (Levy-Lahad et al 1995a, b; Li et al 1995; Rogaev et al 1995). Affected individuals in the Volga German families were heterozygous at codon 141, resulting in an Asn-Ile substitution; in the Italian pedigree, the PS2 variant Met239Val cosegregates with early-onset FAD (Rogaev et al 1995).

## PROTEINS IMPLICATED IN AUTOSOMAL DOMINANT FAMILIAL AD

### *APP*

**STRUCTURE, LOCALIZATION, AND PROCESSING** The APP gene (Kang et al 1987, St George-Hyslop et al 1987, Tanzi et al 1988) encompasses ~400 kb of DNA (Lamb et al 1993), contains 19 exons, and gives rise to several alternatively spliced APP mRNA that encode A/ $\beta$ -containing proteins between 677 and 770 amino acids (Kang et al 1987, Kitaguchi et al 1988, Ponte et al 1988, Tanzi et al 1988, Konig et al 1992). Several APP isoforms contain a region encoded by exon 7 that is structurally and functionally homologous to the Kunitz family of protease inhibitors (KPI) (Kitaguchi et al 1988, Ponte et al 1988, Tanzi et al 1988).

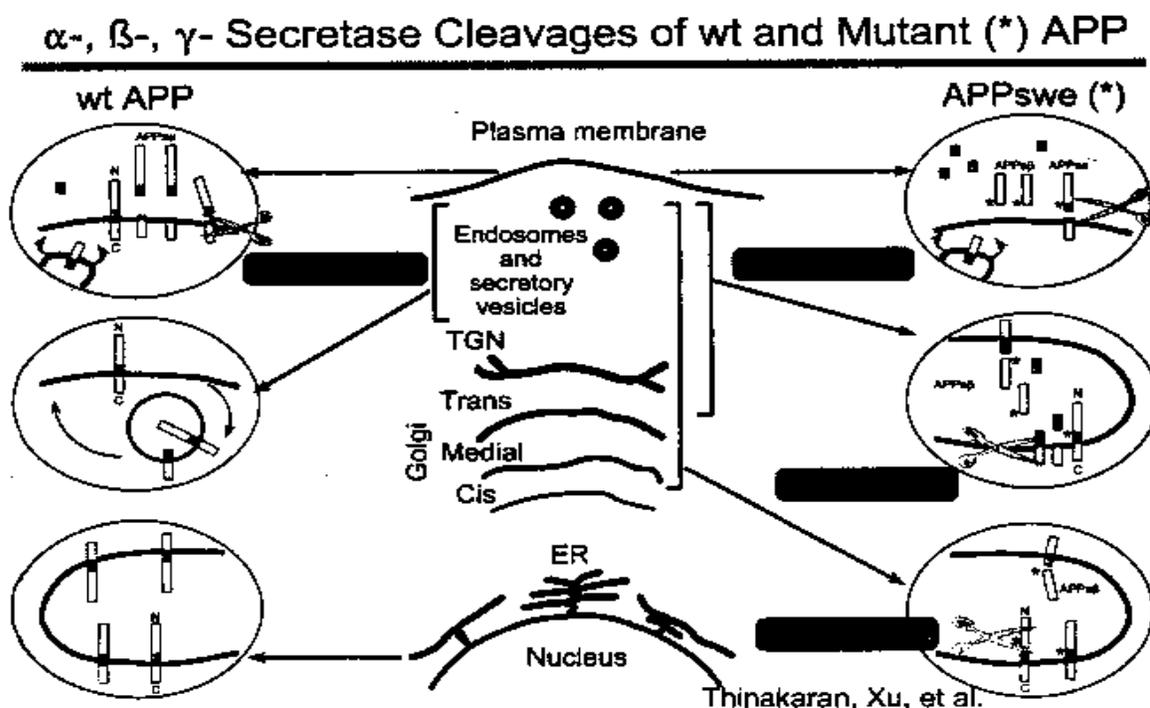
KPI-containing APP isoforms are expressed in virtually all peripheral tissues and in adult primate brain (Koo et al 1990b). In contrast, APP-695 is particularly enriched in the nervous system of rodents (Koo et al 1990b, Sisodia et al 1993). In the central and peripheral nervous systems, APPs are present in neurons (and, to a lesser extent, in glia); in axons of nerve cells, APPs are transported by the fast anterograde system (Koo et al 1990a, Sisodia et al 1993). It has been suggested that APP may play a role in the outgrowth or maintenance of axons or nerve terminals, a view supported by studies suggesting that APP colocalizes with B1 integrins at focal contact sites of differentiating neuronal cells (Yamazaki et al 1997) and is capable of enhancing neurite outgrowth (Milward et al 1992, Qiu et al 1995). In some experimental settings, APP appears to participate in trophic or neuroprotective influences (Mattson et al 1993).

APPs are typical type-I integral membrane proteins that contain an N-terminal signal peptide, a large ectodomain with sites for N-glycosylation, a single membrane-spanning helix, and a short cytoplasmic domain. In cultured mammalian cells, APPs mature through the constitutive secretory pathway and are modified by the addition of both N- and O-linked carbohydrates and sulfate moieties (Weidemann et al 1989). The APP ecto- and cytoplasmic domains are phosphorylated (Hung & Selkoe 1994, Suzuki et al 1997, Walter et al 1997a), but the functional implications of these processes are unknown. Newly synthesized APP molecules appear at the cell surface (Weidemann et al 1989, Haass et al 1992a, Sisodia 1992); some of these molecules are cleaved endoproteolytically within the AB sequence by APP  $\alpha$ -secretase (APP<sup>s</sup>) to release the ectodomain of APP, including residues 1-16 of A $\beta$ , into the culture medium (in vitro) or into the cerebrospinal fluid (in vivo) (Palinert et al 1989a,b; Weidemann et al 1989; Esch et al 1990; Sisodia et al 1990; Wang et al 1991). The cleavage of APP within the A $\beta$  domain precludes the formation of A $\beta$ . The substrate requirements for  $\alpha$ -secretase processing are highly unusual; the enzyme exhibits relaxed specificity at the site of cleavage, requires an  $\alpha$ -helical domain proximal to the cleavage site, and cleaves substrates at a defined distance from the plasma membrane (Sisodia 1992, Sahasrabudhe et al 1992). Interestingly, several first messengers (e.g. phorbol esters, cholinergic agonists, and other neurotransmitters) activate the phospholipase

C/protein kinase C-dependent pathway and enhance the secretion of APP<sup>s</sup> into the conditioned medium of cultured cells (Buxbaum et al 1992, Nitsch et al 1992). The activation of APP<sup>s</sup> release appears not to be the result of direct phosphorylation of the APP cytoplasmic domain (Hung & Selkoe 1994) but, rather, to be the result of enhanced budding of APP-containing nascent vesicles from the trans-Golgi network and trafficking to the plasma membrane (Xu et al 1995), the site of  $\alpha$ -secretase activity (Haass et al 1992a, Sisodia 1992).

**AB FORMATION** Early studies demonstrating that APP normally undergoes endoproteolysis by  $\alpha$ -secretase led to the assumption that, in disease settings, A $\beta$  was generated via aberrant proteolytic processing of the precursor. This model was revised when A $\beta$  peptides were detected in the conditioned medium of cultured cells (Haass et al 1992b, Seubert et al 1992, Shoji et al 1992, Busciglio et al 1993) and in the cerebrospinal fluid of cognitively normal individuals (Shoji et al 1992, Seubert et al 1993).

A $\beta$  can be generated by several pathways, not mutually exclusive, that involve the endoproteolytic cleavage of APP by hitherto uncharacterized activities, termed  $\beta$ - and  $\gamma$ -secretase, which generate the N and C termini of the peptide, respectively (Haass & Selkoe 1993) (Figure 3). The cellular sites of AB production have been thoroughly investigated in cell culture systems. Initial studies indicated that a fraction of cell-surface APP is subject to endocytosis in events mediated by a signal, YENPrY, in the cytoplasmic tail with APP (Golde et al 1992, Haass et al 1992a, Lai et al 1995). Endosomal/lysosomal processing of APP leads to the production of fragments that contain the APP C terminus and entire At region and, hence, are potentially amyloidogenic (Golde et al 1992, Haass et al 1992a). Despite the initial excitement generated by the discovery of these AB-containing fragments, several lines of evidence now suggest that the lysosomal degradation of APP is unlikely to contribute to the production of A $\beta$ : Kinetic studies show that AB is released in parallel to soluble APP (APP<sup>s</sup>) (Busciglio et al 1993); A $\beta$  is not detected in purified lysosomes (Haass et al 1992b); A $\beta$  production is not inhibited by leupeptin, an inhibitor of lysosomal protease function (Haass et al 1992b); and, finally, A $\beta$  is released by cultured fibroblasts from patients with I-cell disease, in which proteases fail to target to lysosomes. However, agents that interfere with pH gradients (i.e. ammonium chloride and chloroquine) inhibit the production of A $\beta$  (Haass et al 1992b, Shoji et al 1992), suggesting that A $\beta$  may be generated in acidic compartments (i.e. endosomes or late Golgi). Furthermore, cells that express APP deleted of the entire cytoplasmic tail (APPAC) release lower levels of soluble A $\beta$  (Citron et al 1992), suggesting that the internalization of APP from the cell surface and subsequent recycling to the plasma membrane may be responsible for the generation of A $\beta$ . Two lines of evidence are consistent with this idea: Secreted A $\beta$  can be generated from [125I] surface-labeled APP (Koo & Squazzo 1994), and the surface APP "tagged" with either monoclonal antibodies or biotin can be recycled to the plasma membrane after endocytosis (Koo et al 1996). These studies offered a model wherein  $\beta$ -secretase cleavage occurs within endocytic compartments, and  $\gamma$ -secretase cleavage of the residual 100-amino acid membrane-bound fragment within the APP transmembrane domain occurs virtually simultaneously with the formation and release of A $\beta$ . Although the majority of A $\beta$  appears to be generated in the endosomal recycling pathway, a fraction of secreted A $\beta$  species are also generated in a secretory pathway. Moreover, it is now clear that ~90% of secreted A $\beta$  peptides are A $\beta$ 40, a fairly innocuous, soluble form of the peptide. The remaining (~10%) secreted A $\beta$  peptides are A $\beta$ 42 and A $\beta$ 43--species that are highly fibrillogenic and are deposited early and selectively in amyloid plaques in individuals with AD and Down's syndrome (see below).



*Figure 3* Model depicting sites of  $\alpha$ - and  $\beta$ -secretase cleavage of wild-type amyloid precursor protein (wt APP) and APP with the Swedish mutation (APP<sup>swE</sup>). The *middle panel* depicts selected cellular compartments of the central vacuolar pathway involved in APP trafficking/processing. For wt APP, secreted APP  $\alpha$ -secretase (APP<sup>s</sup>) are generated by cleavage of full-length molecules by  $\alpha$ -secretase on the plasma membrane, and secreted  $\beta$ -amyloid protein (A $\beta$ ) occurs via the endocytic recycling of plasma membrane-bound APP. For APP<sup>swE</sup>,  $\beta$ -secretase cleaves full-length membrane bound molecules in the medial Golgi and compartments proximal to the plasma membrane. [Modified from Thinakaran et al (1996).]

Although it has not been established whether A $\beta$  42(43) are generated in the endocytic recycling pathway, preliminary studies from independent laboratories have offered support for the idea that these peptides may be uniquely produced in the endoplasmic reticulum (Cook et al 1997, Hartmann et al 1997). Furthermore, the recent demonstration that a broad specificity cathepsin inhibitor, MDL28170, selectively inhibits A $\beta$  40 production indicates that the  $\gamma$ -secretases are responsible for generating A $\beta$  40 and that A $\beta$  42(43) are pharmacologically distinct (Citron et al 1996). Despite the important insights drawn from investigations of APP trafficking and A $\beta$  production in nonneuronal cultured cells, the mechanisms and cellular sites of A $\beta$  production by neurons remain a mystery. Intriguingly, in cultured rodent hippocampal and peripheral sympathetic neurons, cell-surface APP is internalized from distal axons or terminals via a novel rab5-containing sorting intermediate compartment (Ikin et al 1996, Marquez-Sterling et al 1997) and is transported transcytotically back to perikarya (Yamazaki et al 1995). The fates of APP retrogradely transported to perikarya are not known.

**CONSEQUENCES OF APP MUTATIONS AND PATHOGENICITY OF A $\beta$  PEPTIDES** The presence of the Ala-Gly substitution at amino acid 692 (Hendricks et al 1992) reduces the efficacy of  $\alpha$ -secretase processing; leading to considerable micro-heterogeneity of secreted A $\beta$  species, including the appearance of more hydrophobic species. Cultured cells that express APP with the Swedish

mutation (APP<sup>swe</sup>) secrete six to eightfold higher levels of ~4-kDa A $\beta$  peptides as compared to cells that express wild-type (wt) constructs (Citron et al 1992). The elevated secretion of A $\beta$  from cells that express APP<sup>swe</sup> is likely caused by the initial endoproteolytic cleavage of APP at the  $\beta$ -secretase site during transit of the precursor through the medial and *trans* Golgi compartments (Perez et al 1996, Thinakaran et al 1996b) and nascent post-TGN vesicles (Haass et al 1995), followed by  $\gamma$ -secretase cleavage of the remaining C-terminal ~100 amino acids that contain the entire A $\beta$  peptide. These A $\beta$ -generating events occur in late-processing compartments or at the cell surface. Consistent with this concept is the observation that A $\beta$  production occurs in cell-free systems (consisting of semipurified TGN preparations from cells that express APP<sup>swe</sup>) under conditions that inhibit the formation of nascent post-TGN vesicles (Xu et al 1997).

Cells that express APP harboring the "717" substitutions (near the  $\gamma$ -secretase site) do not appear to secrete higher levels of A $\beta$  but, rather, secrete a higher fraction of longer A $\beta$  peptides (i.e. extending to A $\beta$  residue 42) relative to cells that express wt APP (Suzuki et al 1994). Cells that express APP<sup>swe</sup> secrete higher levels of A $\beta$ , with levels of A $\beta$  42 peptides increasing accordingly (Suzuki et al 1994). Elevations of levels of longer A $\beta$  peptides are important because physicochemical studies have indicated that amyloid formation is a nucleation-dependent phenomenon and that the C terminus may be a critical determinant of the rate of amyloid formation (Jarrett & Lansbury 1993). Significantly, immunocytochemical and biochemical studies performed with antibodies uniquely specific for A $\beta$ 40 or A $\beta$ 42 have shown that A $\beta$  deposition in the brains of cases of AD begins with A $\beta$ 42(43) (Iwatsubo et al 1994, Letoere et al 1996a).

Biophysical studies indicate that A $\beta$ 42 initiates rapid and complete aggregation of peptides as compared to A $\beta$ 40. In addition, A $\beta$  42 fibrils can apparently recruit both AB40 and AB42 into a structured assembly. These phenomena appear to play a crucial role in AD because the longer AB42 is preferentially deposited in the disease (Roher et al 1993, Iwatsubo et al 1994, Letoere et al 1996a). Experimentally, A $\beta$  aggregation can be modulated by pH and by metal ion concentration, prompting speculation that the exposure of endocytosed A $\beta$  to acidic vacuoles or of extracellular A $\beta$  to metal ions (e.g. zinc) may contribute to its deposition in AD. However, the influences of pH- and metal-induced A $\beta$  aggregation on the pathophysiology of AD are unknown.

The biophysical state of AB has been implicated as an explanation for the wide variability in its activity as a neurotoxin for cells in culture. Indeed, the aggregation state of A $\beta$  has been reported to be a crucial factor in A $\beta$  neurotoxic activity in vitro (Pike et al 1993), and this neurotoxic activity can be mimicked by other aggregated or fibrillar amyloidogenic proteins that have primary sequences unrelated to A $\beta$  (May et al 1993). To date, the relevance of in vitro models of A $\beta$  neurotoxicity for human AD remains unclear. Efforts to extend this line of investigation to the rodent and primate brain in vivo have produced inconsistent results (Price et al 1992, Podlisny et al 1997). Given the large number of substances associated with brain amyloid plaques in addition to A $\beta$  [e.g. apoE, clusterin/apoJ, heparan sulfate proteoglycans (Snow et al 1988), and complement (Rogers et al 1988)], it is entirely possible that more relevant mediators of important pathogenic processes may be attributable to minor plaque component(s) and/or to local responses (i.e. astrocytes, inflammatory cells) to deposits of A $\beta$ . These possibilities can be assessed in recently developed transgenic mouse models (see below) that reproduce some of the pathological features of AD in vivo (Games et al 1995, Hsiao et al 1996).

### *Presenilins 1 and 2*

**STRUCTURE, PROCESSING, AND LOCALIZATION** Using a variety of secondary structure algorithms, PS 1 was predicted to contain between seven (Sherrington et al 1995) and nine transmembrane domains and included a hydrophilic acidic "loop" region encompassing amino acids 262--407. The topology of PS 1 has been recently clarified by two strategies: First, putative

"transmembrane helices" were tested for their ability to export a protease-sensitive substrate across a lipid bilayer; and, second, the plasma membrane of cultured cells that express human (Hu)PS 1 were selectively permeabilized, and the accessibility of antibodies specific for the N terminus, the loop, and the C terminus to cognate epitopes was analyzed by indirect immunofluorescence microscopy. These studies established that the N terminus, loop, and C terminus of PS 1 are oriented towards the cytoplasm (Figure 2) (Doan et al 1996, De Strooper et al 1997). Similarly, the topology of the *Caenorhabditis elegans* presenilin ho-mologue, termed sel-12 (see below), was determined using a series of sel-12  $\beta$ -galactosidase chimeras, an approach that relies on the observation that  $\beta$ -galactosidase is active in the cytoplasm of cells and is inactive in the lumen of membrane compartments. The deduced topology of sel-12 indicated that the protein spans the membrane eight times, with N and C termini being exposed to the cytosol (Li & Greenwald 1996). More recently, Lehmann et al (1997) provided evidence for a six-transmembrane domain structure of presenilins, wherein the C-terminal hydrophobic domains are associated with the cytosolic face but do not span the lipid bilayer.

Although the topology of PS2 has not been determined, it is highly likely that PS2 adopts a configuration not unlike PS1 and sel-12. Significantly, the cytosolic domains of PS1 and PS2 are highly divergent (< 10% identity in the N-terminal 70 amino acids and between amino acids 305-375 in the loop), suggesting that these regions mediate cell- or PS-specific functions via differential interactions with proteins in the cytoplasm. Efforts aimed at the identification and characterization of molecules that interact with PS-specific cytosolic domains will be critical for the elucidation of the biological function(s) of this novel class of polytopic membrane' proteins. In this regard, Zhou et al (1997) utilized a yeast two-hybrid approach to identify  $\gamma$ -catenin as an interaction with the PS 1 loop domain. Interestingly,  $\gamma$ -catenin is a member of a larger family of catenins related to a *Drosophila*-protein termed armadillo involved in inductive signaling events during development.

The posttranslational processing of PS 1 has been investigated in cultured cells and in vivo. Biochemical studies indicate that PSs are not substrates for sulfation, glycosylation, or acylation (Cook et al 1996, De Strooper et al 1997). However, serine residues in the N terminus of PS2 (De Strooper et al 1997) and serine residues in the cytosolic loop domain of PS1 (De Strooper et al 1997, Seeger et al 1997, Walter et al 1997b) are in vivo substrates for phosphorylation, the physiological significance of which is not understood. In this regard, PS1 phosphorylation is enhanced in response to activation of either protein kinase C or cAMP-dependent protein kinase or to the inhibition of protein phosphatase 1 or 2A (De Strooper et al 1997, Seeger et al 1997, Walter et al 1997b).

The most surprising aspect of PS 1 metabolism is that, although PS 1 is synthesized as an ~42- to 43-kDa polypeptide, the preponderant PS 1-related species that accumulate in cultured mammalian cells and in the brains and systemic tissues of rodents, PS 1 transgenic mice, primates, and humans are ~27- to 28-kDa N-terminal and ~ 16- to 17-kDa C-terminal derivatives (Lee et al 1996, Thinakaran et al 1996a, Podlisny et al 1997, Walter et al 1997b). Epitope mapping studies suggest that PS 1 is cleaved within a region that encompasses amino acids 260--320, a domain in which >50% of identified FAD-linked PS 1 mutations occur. Recent studies suggest that cleavage may be hererogenous, occurring between amino acids 292 and 299 (Podlisny et al 1997). These results are consistent with the demonstration that the FAD-linked PS 1A<sub>E9</sub> variant, which lacks amino acids 290-319, fails to be cleaved (Thinakaran et al 1996a).

The accumulation of ~17-kDa and ~27-kDa Hu-specific PS 1 derivatives in the brains of transgenic mice that express HuPS 1 is highly regulated and saturable (Thinakaran et al 1996a, Lee et al 1997); levels of PS 1 derivatives are disproportionate to levels of transgene-derived mRNA or full-length HuPS 1. The stoichiometry of accumulated ~17-kDa and ~27-kDa PS 1 fragments is 1:1 in nontransgenic and transgenic mouse brains; this ratio is independent of the level of transgene-derived HuPS 1 mRNA expression (Thinakaran et al 1996a). Mechanism(s) involved in the regulation of the

levels of accumulated PS 1 derivatives have not been established. Nevertheless, in overexpressing cell systems, it appears that only a small fraction of newly synthesized PS2 is converted to fragments and that the remaining full-length proteins are polyubiquitinated and degraded by a lactacystin-sensitive proteasome pathway (Kim et al 1997). Two lines of evidence indicate that N- and C-terminal PS1 derivatives are coresident: In cultured mammalian cells, these fragments can be specifically cross-linked using a membrane-permeable sulfhydryl-cleavable cross-linking agent, DSP; and, the two fragments can be coimmunoprecipitated from mild detergent lysates of cultured cells or mammalian brain (G Thinakaran, CL Harris, T Ratovitski, F Davenport, HH Slunt, et al, submitted for publication). Moreover, gel filtration chromatography and sucrose density gradient fractionation of PS 1 isolated from cells reveal that PS 1 N- and C-terminal fragments appear to remain associated in larger complexes of ~100 kDa (Seeger et al 1997). It is not presently clear whether the coisolated fragments are in homomeric or heteromeric assemblies.

A conserved feature of the topology models for the PS homologues is that the site for endoproteolytic cleavage is located in the cytosolic compartment. At present, neither the identity of the protease nor the physiological significance of PS 1 proteolysis is known. However, in view of the demonstration of a paucity of full-length PS 1 and highly regulated accumulation of processed derivatives *in vivo*, it is highly likely that PS 1 fragments are the functional units (Thinakaran et al 1996a). Moreover, HuPS2 (Citron et al 1997, De Strooper et al 1997, Kim et al 1997, Tomita et al 1997) and sel-12-B-galactosidase chimeras (Li & Greenwald 1996) are also subject to endoproteolytic cleavage. This observation indicates that endoproteolysis of the protein is a highly conserved process and, arguably, a processing event that regulates the accumulation of fragments.

PS 1 and PS2 mRNA are expressed in a variety of peripheral tissues and in the brain (Alzheimer's Disease Collaborative Group 1995, Rogaev et al 1995, Sherrington et al 1995, Lee et al 1996). Although the structural conservation and relatively ubiquitous expression pattern of PS 1 and PS2 mRNA suggest some degree of functional redundancy, differences exist in relative levels of expression, suggesting that PS 1 and PS2 may play different roles in tissue- or development-specific processes. Northern blotting has indicated that PS2 mRNA are expressed at low levels relative to PS 1 mRNA (Rogaev et al 1995), but quantitative RT-PCR studies have revealed that PS 1 and PS2 transcripts are expressed at significantly different levels among tissues and during brain development (Lee et al 1996). In the brains of adult mammals, both PS 1 and PS2 transcripts are expressed in many neuronal populations (Lee et al 1996, Suzuki et al 1996), and the mRNA are also present in glial cells (Sherrington et al 1995, Lee et al 1996, Rogaev et al 1995). Notably, nerve cells known to be at risk in AD (i.e. neurons in hippocampal CA fields, in the roedial and cortical amygdala, and in nedcortex) express PS and APP transcripts at high levels, whereas neurons in regions less prone to AD-associated express PSs and APP transcripts at more variable levels (Lee et al 1996).

Immunocytochemical analyses of a variety of cultured nonneuronal cells that express transiently expressed full-length PS 1 and PS2 revealed that the proteins are localized to similar intracellular membranous compartments, including the endoplasmic reticulum, and to varying extents, the Golgi complex (Cook et al 1996, De Strooper et al 1997). In stably transfected cells (in which PS 1 fragments of ~28 and ~18 kDa are preponderant), PS 1 immunoreactivity is restricted to the endoplasmic reticulum (Doan et al 1996). Interestingly, the expression of epitope-tagged PS 1 in a human neuronal cell line, NT2N, using a Semiki Forest Virus delivery system, revealed that PS 1 was localized primarily to the rough endoplasmic reticulum in cell bodies and dendrites but was excluded from axons and the cell surface (Cook et al 1996). More recently, light microscopic immunocytochemical studies of rodent (Lee et al 1996), primate (Lah et al 1997), and human brains using antibodies selective for the N- or C-terminal PS 1 fragments revealed that PS 1 was present in all brain regions, with the strongest labeling in neurons and the neuropil, including axons and dendrites; weaker immunoreactivity was present in glial cells. Subcellular fractionation of monkey

cortex revealed PS1 enrichment in nonsynaptic vesicle membrane compartments (Lah et al 1997). Notably, electron microscopic immunocytochemistry using an antibody specific for the PS 1 N-terminal fragment disclosed selective PS 1 immunoreactivity on cytoplasmic surfaces of smooth membranous organelles in cell bodies of neurons, suggesting localization in the endoplasmic reticulum-Golgi intermediate compartment and less-prominent localization in coated transport vesicles (Lah et al 1997). In the neuropil, PS1 immunoreactivity was present in dendritic spines and occasional presynaptic structures. In dendritic spines, PS1-immunoreactive structures had the general appearance of smooth tubular membranes or vesicles that resembled dendritic compartments of the smooth endoplasmic reticulum; no staining was observed on presynaptic structures, including synaptic vesicles (Lah et al 1997).

The first major insight regarding PS function emerged with the discovery of a homologous gene in *C. elegans*, termed sel-12; mutant alleles of sel-12 were uncovered as suppressors of a hypomorphic multivulval phenotype in *C. elegans* linked to hyperactivity of the *C. elegans* Notch homologues lin-12 and glpl (Levitan & Greenwald 1995). Notch and lin-12/glpl are transmembrane receptors required for the specification of cell fate and lateral inhibition during development (Artavanis-Tsakonas et al 1995). Although details regarding the molecular mechanisms by which sel-12 facilitates signaling mediated by lin-12 have not been established, two models have been proposed: First, sel-12 could regulate lin-12 trafficking and cell surface expression; or, second, sel-12 could act in a signaling capacity to modulate pathways activated following the binding of cognate ligands to lin-12. The extremely high amino acid homology between the PS and sel-12, particularly in the first six transmembrane domains and the ~90 C-terminal residues, led to the prediction that related proteins would be functionally interchangeable. Consistent with this hypothesis, an egg-laying (egl) defect associated with loss of sel-12 function in *C. elegans* is rescued efficiently by the expression of HuPS 1 and -PS2; the rescue efficiency of HuPS was essentially indistinguishable to transgenic worms that express sel-12 (Levitan et al 1996, Banmeister et al 1997). Notably, the egl defect was only weakly rescued in transgenic worms that express several human FAD-linked PSI variants (Levitan et al 1996, Banmeister et al 1997), suggesting that PS 1 missense variants behaved as loss-of-function alleles. Interestingly, the PS 1 AE9 variant showed considerable rescue activity relative to other PS 1 missense variants. Although the significance of this finding is unclear, it suggests that endoproteolytic cleavage is not obligatory for PS 1 function in this developmental paradigm (Levitan et al 1996, Banmeister et al 1997).

Although the *C. elegans* rescue experiments provided compelling evidence that HuPS1 and HuPS2 could substitute for sel-12, the role of PSs in mammalian development was uncertain. In situ hybridization studies and RT-PCR approaches in mouse embryos revealed that PSs are expressed in an ubiquitous manner during embryonic development [i.e. as early as embryonic day (E) 8.5] (Lee et al 1996). However, the general spatial and temporal expression patterns of presenilin mRNA do not directly coincide with the expression patterns of any specific member of the known mammalian Notch homologues. These results suggested that during mammalian development, PS1 function is not limited to Notch signaling alone (Lee et al 1996). The results of PS1 gene-targeting studies are discussed below.

**CONSEQUENCES OF PS MUTATIONS** The metabolism of several PS1 variants containing FAD-linked missense mutations has been examined in cultured cells and in transgenic mice. In cultured cells, the PS1AE9 variant failed to be cleaved (Thinakaran et al 1996a), but the human M146L, H163R, A246E, E280A, L286V, L392V, or C410Y PS1 variants and the N141I PS2 variant are efficiently processed into N- and C-terminal derivatives (Borchelt et al 1996, Citron et al 1997, De Strooper et al 1997, Kim et al 1997, Podlisny et al 1997, Tomita et al 1997). The HuPS1 A246E, M146L, M146V, H163R, and L286V variants are also efficiently cleaved into two fragments in brains

of transgenic mice (Borchelt et al 1996, Duff et al 1996, Citron et al 1997, Lee et al 1997). Hence, full-length FAD-linked variants with missense substitutions undergo endoproteolysis in a manner not unlike that described for wt PS1. Nevertheless, the accumulation of full-length PS1 has been reported in the brain in two individuals with FAD harboring a G209V PS1 mutation. Curiously, whereas HuPS1 derivatives in the brains of mice that express the A246E or M146L mutant PS1 accumulate to saturable levels and to 1:1 stoichiometry, there is a quantifiable ~ 1.5-fold increase in the levels of mutant derived fragments relative to those generated from wt HuPS1 (Lee et al 1997). Although parallel increases in levels of C-terminal fragments derived from mutant PS1 may seem surprising (because both the A246E and M146L mutations reside in the N-terminal ~28-kDa derivative), these observations are consistent with the hypothesis that the accumulation of PS1 N- and C-terminal derivatives is coordinately regulated. It is not known whether the observed elevation in the "set-point" in accumulated levels of mutant PS-derived fragments is the result of enhanced endoproteolytic processing of mutant presenilin and/or greater stability of mutant PS1-derived fragments (Lee et al 1997). It is important to note that elevations in PS1 fragments or full-length PS1 have not been detected in brains of additional cases with PSI-linked FAD (Citron et al 1997). However, it is conceivable that confounding antemortem events or postmortem variables may mask relatively subtle differences in accumulated PS1 or its fragments in the brains of affected individuals. Nevertheless, recent studies have documented that, in brain extracts from an individual harboring the FAD-linked PS2 N141I mutation, the C-terminal derivative of PS2 accumulates to approximately twofold higher levels as compared with the C-terminal derivative in brain homogenates from three unaffected family members.

The mechanisms by which FAD-linked PS1 and PS2 variants cause FAD are unclear. Nevertheless, the incomplete rescue of egl by FAD-linked PS1 variants suggests that these mutant PSs act as loss-of-function alleles. However, the absence of nonsense or frameshift mutations that lead to truncated PS1/PS2 supports the notion that AD is caused not by the loss but by the gain of deleterious properties of mutant polypeptides. In this regard, studies have suggested that PS2 may participate in neuronal apoptosis (Wolozin et al 1996) the transient overexpression of full-length PS2 in nerve growth factor-differentiated PC12 cells led to a pertussis toxin-sensitive increase in apoptosis induced by trophic factor withdrawal or treatment with A $\beta$ . Moreover, the expression of cDNA that encode antisense PS2 mRNA protected against apoptotic cell death induced by trophic factor withdrawal or glutamate-induced cell death. In support of these investigations, PC12 cells that express the L286V mutant PS1 exhibit significant increases in oxidative stress, increased Ca<sup>2+</sup> following exposure to A $\beta$ , and increased susceptibility to apoptosis induced by trophic factor withdrawal and AB (Guo et al 1997). Collectively, these studies suggest that the expression of mutant PS may influence neurodegeneration. On the other hand, studies of transgenic mice expressing mutant PSI (Borchelt et al 1996, Duff et al 1996, Lee et al 1997) have failed to disclose any cellular abnormalities consistent with apoptosis (see below).

### *Presenilin and A $\beta$*

The most provocative insights pertaining to the mechanisms by which mutant PS1 predispose carriers to FAD emerged initially from studies that examined the conditioned medium from fibroblasts or the plasma from affected members of pedigrees with PS1/PS2-linked mutations. Highly sensitive sandwich ELISA assays with antibodies specific for the C terminus of A $\beta$ 40 and A $\beta$ 42 (Suzuki et al 1994) revealed that the ratio of A $\beta$ 42(43)/A $\beta$ 40 in affected individuals was significantly elevated relative to unaffected family members (Scheuner et al 1996). These data suggest that FAD-linked PS1/PS2 variants influence processing at the  $\gamma$ -secretase site and cause AD by increasing the extracellular concentration of highly amyloidogenic A $\beta$ 42(43) species, thus fostering A $\beta$  deposition in the brain.

## Mutant Genes in Familial Alzheimer's Disease

The influence of wt and mutant PS1 and PS2 on A $\beta$ 40 and A $\beta$ 42(43) production has been evaluated in transfected mammalian cells and the brains of transgenic mice (Borchelt et al 1996, Duff et al 1996, Citron et al 1997, Tomita et al 1997). Sandwich ELISA analysis of the conditioned medium of cells that coexpress HuAPP with either wt or mutant PS (Borchelt et al 1996, Citron et al 1997, Tomita et al 1997) have clearly documented that a variety of mutant PS 1 variants, including A246E, M146L, AE9, L286V, L392V, and H163R, and the PS2 variant N141I, influence APP processing in a manner that elevates levels of A $\beta$ 42(43) relative to cells expressing wt PS. Compared to cells that express wt PS1, the ratio of A $\beta$ 42(43)/A $\beta$ 40 was elevated by ~1.5- to 3-fold.

### GENE-TARGETED MICE

#### *APP Knockout Mice*

In an effort to clarify the roles of APP in vivo, Zheng and colleagues (Zheng et al 1995) generated mice with functionally inactivated alleles of APP. When compared to hemizygous APP or wt littermates, homozygous APP knockout mice were fertile and viable but exhibited subtle decreases in locomotor activity and forelimb grip strength as well as reactive astrogliosis. The absence of substantial phenotypes in APP knockout mice may be related to functional redundancy provided by homologous amyloid precursor-like proteins (APLP1 and APLP2), molecules that are expressed at high levels and have developmental and cellular distributions similar to APP (Wasco et al 1992, 1993; Slunt et al 1994).

#### *PS1 Knockout Mice*

To examine the in vivo role of PS 1 in mammalian development, mice with a targeted disruption of the PS1 gene were generated (Shen et al 1997, Wong et al 1997). Homozygous mutant mice failed to survive beyond the first 10 min after birth. The most striking phenotype observed in PS1<sup>-/-</sup> embryos was a severe perturbation in the development of the axial skeleton and ribs. The failed development of the axial skeleton in PS 1<sup>-/-</sup> animals was traced to defects in somitogenesis; in E8.5 and E9.5 embryos, somites were irregularly shaped and misaligned along the entire length of the neural tube and largely absent at the caudalmost regions. The abnormal somite patterns in PS1<sup>-/-</sup> embryos are highly reminiscent of somite segmentation defects described in mice with functionally inactivated Notch 1 and Dll 1 (encoding a Notch ligand) alleles (Conlon et al 1995, Hrabe de Angelis et al 1997). Remarkably, the expression of mRNA that encodes Notch 1 and Dll 1 is reduced considerably in the presomitic mesoderm of PS 1<sup>-/-</sup> mice (Wong et al 1997). In addition, all PS 1<sup>-/-</sup> embryos exhibited intraparenchymal hemorrhages after day 11 of gestation. It has also been reported that, in the brains of PS 1<sup>-/-</sup> mice, the ventricular zone is thinner by day 14.5 and the massive neuronal loss in specific subregions is apparent after day 16.5. These observations have been interpreted to indicate that PS1 is required for normal neurogenesis and neuronal survival (Shen et al 1997). In the midst of the confounding cerebral hemorrhage, however, the neuronal phenotypes remain unsettled. A more satisfying model, in which the PS1 gene is ablated in a conditional manner, is required to clarify this issue.

### TRANSGENIC MICE

#### *APP Transgenic Mice*

To generate animal models of A $\beta$  amyloidogenesis and the associated histo-pathology of AD, many groups have created transgenic mice that express wt APP, FAD-linked APP variants, C-terminal fragments of APP, or A $\beta$  itself (Kammesheidt et al 1992; Neve et al 1992; Buxbaum et al 1993; Lamb et al 1993; Hsiao et al 1995, 1996; LaFerla et al 1995). These efforts have produced lines of transgenic

mice, but only two of these recapitulate some of the neuropathological features of human AD (Games et al 1995, Hsiao et al 1996). Studies of these lines of transgenic mice described below, as well as lines produced in future experiments, will be valuable for investigating mechanisms for testing therapies.

In one line of mice, the PDGF  $\beta$ -promoter was used to drive the expression of a HuAPP minigene that encodes the FAD-linked APP (717V6F) mutation in an outbred strain; the construct contained portions of APP introns 6-8, which allow alternative splicing of exons 7 and 8. Levels of HuAPP mRNA and protein significantly exceeded levels of endogenous APP. The transcripts encoded the three major splicing variants, particularly the KPI-coding form, and levels of the transgene product were approximately four to five times higher than endogenous APP (Games et al 1995). The brain showed diffuse A $\beta$  deposits and plaques with tau-negative dystrophic neurites displayed around A $\beta$  cores (Masliah et al 1996).

In a second line of transgenic mice, the hamster PrP promoter overexpressed HuAPP-695.swe (Hsiao et al 1996). At three months of age, these mice showed normal learning and memory in spatial reference and alternation tasks, but by 9-10 months of age, they were impaired on these tasks. In the brain, levels of A $\beta$ 40 and A $\beta$ 42 were increased 5-fold and 14-fold, respectively; dystrophic neurites and A $\beta$  deposits were conspicuous in amygdala, hippocampus, and cortex. Similar strategies using a mouse PrP promoter have recently produced two additional lines of HuAPP<sup>swe</sup> transgenic mice that develop A/5 deposits at ~18-20 months of age (DR Boreheir, SS Sisodia & DL Price, personal observations).

In all of these lines of APP transgenic animals showing A/5 deposits, the mutant APP transgene was expressed at high levels in nervous tissue, and the mice lived well into adult life. Findings in the APP transgenic mice are consistent with studies of other successful transgenic models that have reproduced familial amyotrophic lateral sclerosis, prion diseases, and SCA-1 by overexpressing mutant superoxide dismutase 1 (SOD1), PrP, and ataxin-1, respectively (Hsiao et al 1990, Burchright et al 1995, Wong et al 1995).

### *PS1 and APP Transgenic Mice*

In the brains of young (two- to three-month-old) transgenic mice that express HuPS 1 harboring FAD-linked mutations, the ratio of A $\beta$ 42:40 is increased (Borebelt et al 1996, Duff et al 1996, Citron et al 1997). In our studies, we coexpressed A246E HuPS 1 and a chimeric mouse/HuAPP695 harboring a HuA $\beta$  domain, as well as mutations (K595N, M596L) linked to APP<sup>swe</sup> FAD pedigrees (Borchelt et al 1996). At 12 months of age, transgenic animals that coexpressed A246E HuPS 1 and APP<sup>swe</sup> contained numerous amyloid deposits (Borchelt et al 1997), many of which were associated with dystrophic neurites and reactive astrocytes. Parallel analyses of brains from age-matched animals that express APP695.swe alone or mice that express A246E HuPS 1 alone were free of amyloid deposits (Borebelt et al 1997). These data demonstrate convincingly that the A246E HuPS 1 acts synergistically with APP<sup>swe</sup> to accelerate the rate of amyloid deposition. Neither overt behavioral (up to 16 months) nor neuropathological (up to 12 months) alterations have been observed in mice that express A246E HuPS1 alone. Our findings suggest that the principal mechanism by which mutations in PS 1 cause disease is through elevating extracellular concentrations of A $\beta$ 42, thereby accelerating the deposition of amyloid.

## CONCLUSIONS

The discovery that mutations in genes that encode APP, PS1, and PS2 are linked to FAD has ushered in a new and exciting era of research aimed at clarifying the relationships of genetic abnormalities to the pathogenesis of AD. In autosomal dominant FAD, other mutant genes await discovery. Moreover,

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as exemplified by studies of the roles of apoE allele types in late-onset AD, other genetic factors undoubtedly play significant roles in late-onset disease. The development of in vitro and in vivo paradigms aimed at defining the mechanisms of neurotoxicity, neurodegeneration, and cytoskeletal abnormalities, taken together with recent discoveries relevant to defining the cellular and molecular biology of APP and PS, have begun to have significant impacts on our future understanding of the pathogenic mechanisms for both familial and sporadic AD. Moreover, gene-targeting strategies will help to clarify in vivo functions of genes linked to AD. Finally, several transgenic mouse models offer new opportunities to investigate the evolution and character of AD-type cellular abnormalities, as well as biochemical and cellular mechanisms of disease, and, ultimately, will provide systems to test therapeutic strategies.

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## Alzheimer's Disease

# **Part 5**

## **Treatment Options**

## Alzheimer's Disease

# Treating Alzheimer's disease

## Pharmacologic options now and in the near future

Pierre N. Tariot, MD, Lon Schneider, MD Anton P. Porsteinsson, MD

### PREVIEW

**As the field of knowledge about Alzheimer's disease expands, new strategies for treatment are being explored. In the next 5 to 10 years, an explosion in pharmacotherapeutic options will take place. How will new agents differ from current ones? What will be the added benefits? The authors of this article take a look at current therapies and describe what to expect in the future.**

Although there is no known "first cause" of Alzheimer's disease and no cure, a number of pharmacologic options are available to treat the behavioral and cognitive effects of the disease. Current research based on new hypotheses about the condition's causes and mechanism is expected to lead to rational and innovative advances in treatment. This article, building on a series of previous articles by the authors,<sup>1-6</sup> reviews both current and future pharmacotherapeutic strategies.

### Therapeutic approaches

In general, four therapeutic approaches to Alzheimer's disease can be identified. These attempt to (1) relieve behavioral symptoms associated with dementia, including depression, agitation, and psychosis, (2) relieve cognitive dysfunction to improve memory, language, praxis, attention, and orientation, (3) slow the

rate of illness progression, thereby preserving quality of life and independence, and (4) delay the time of onset of illness.

### Treatment strategies

The pharmacologic treatment strategies for Alzheimer's disease, all of which are based on one or more of the preceding four general approaches, are summarized in Table 1. The behavioral complications of the disorder can be responsive to a variety of medications, and increasing evidence has mounted to guide specific therapy. Therapies also exist for the so-called core symptoms: the cognitive deficits. Several cholinesterase inhibitors are either available or nearing the end of clinical trials. Specifically, tacrine hydrochloride (Cognex) was the first approved treatment for dementia, and donepezil hydrochloride (Aricept) is the first second-generation cholinesterase inhibitor to be approved. These antidementia treatments result in modest improvements in memory and other cognitive functions in the short term, and recent laboratory and clinical evidence suggests that they might also have disease-modifying effects.

### Treat behavioral symptoms

Relieving the behavioral symptoms associated with Alzheimer's disease is an important goal, since the lifetime risk of such symptoms in a

Pierre N. Tariot, MD, Lon Schneider, MD, and Anton P. Porsteinsson, MD Dr Tariot is associate professor, departments of psychiatry, medicine, and neurology, and Dr Porsteinsson is assistant professor, department of psychiatry, University of Rochester School of Medicine, Rochester, New York. Dr Schneider is professor, departments of psychiatry and neurology, University of Southern California School of Medicine, Los Angeles.

Correspondence: Pierre N. Tariot, MD, Department of Psychiatry, University of Rochester School of Medicine, 435 E Henrietta Rd, Rochester, NY 14620.

**Table 1. Pharmacologic treatment strategies for Alzheimer's disease**

**Treat behavioral symptoms**

Antipsychotics (eg, haloperidol [Haldol], lithium, thioridazine HCl [Mellaril], novel agents)  
 Anticonvulsants (eg, carbamazepine, valproic acid [Depakene], Depakote)  
 Trazodone HCl (Desyrel)  
 Buspirone HCl (BuSpar)  
 Selegiline HCl (Eldepryl)  
 Selective serotonin reuptake inhibitors  
 Beta blockers  
 Benzodiazepines

**Restore neurotransmitter function**

Cholinergic Precursors  
 Cholinesterase inhibitors  
 Cholinergic receptor agents

**Other neurotransmitter approaches**

Catecholaminergic  
 Serotonergic  
 Other aminergic  
 Peptidergic

**Enhance cerebral metabolism**

**Stabilize membranes**

**Enhance neuronal sprouting**

**Decrease inflammation**

**Decrease neurotoxins**

**Decrease excitatory amino acids**

**Alter metabolism of key proteins**

patient with dementia approaches 90%.<sup>7</sup>

Behavioral manifestations of dementia include agitation, psychosis, depressive features, anxious features, apathy, and disturbances in sleep and appetite. In most patients, some or all of these manifestations may be amenable to treatment with safe psychotropic medications, including anti-psychotics, antidepressants, and anticonvulsants.

There has been a rapid increase in published information to guide physicians in the use of these medications? This article focuses instead

on the treatments intended to improve cognitive function, delay onset of disease, and slow the disease's progression.

**Restore neurotransmitter function**

Mounting evidence indicates that central cholinergic dysfunction is an early and prominent feature of Alzheimer's disease. The primary implication of the "cholinergic hypothesis" is that potentiation of central cholinergic function should improve the cognitive, and perhaps even the behavioral, manifestations of Alzheimer's disease. There are three general cholinergic approaches to treatment of Alzheimer's disease: precursors, cholinesterase inhibitors, and receptor agents (Table 2).

Precursors: Acetylcholine precursors such as choline and phosphatidylcholine (lecithin) have been used in an attempt to augment acetylcholine synthesis, analogous to the use of a dopamine precursor in Parkinson's disease. Numerous trials, however, have generally yielded negative results?

Cholinesterase inhibitors: These agents delay the intrasynaptic degradation of acetylcholine, thereby presumably prolonging its chemical and functional effects. Cholinesterase inhibitors have been the most widely studied experimental treatment for Alzheimer's disease and are currently the only approved symptomatic treatment. Small but reliable improvement in memory performance has been found after administration of physostigmine salicylate (Antilirium), although individualized dosing appeared to be necessary to optimize this effect.<sup>16</sup> Short duration of action and a high rate of cholinergic side effects (nausea, vomiting, diarrhea, flushing, sweating, bradycardia) are among the limitations of physostigmine. A sustained-release formulation is being developed,<sup>8</sup> There is evidence that long-term administration of physostigmine retards deterioration in cognitive function over time even in patients who fail to improve with short-term administration<sup>2</sup>

Tacrine is a centrally active, reversible, nonspecific cholinesterase inhibitor. An early

case series<sup>10</sup> claimed "dramatic" improvements with tacrine in patients with Alzheimer's disease. Since then, well-designed multicenter trials have shown improvement with tacrine versus placebo in cognitive function and on global clinical scales and indices of daily functioning, leading to marketing approval in the United States and other countries.<sup>11,12</sup> Fewer than a third of patients originally assigned randomly to receive tacrine showed modest, although meaningful, improvement in comparison with those who received placebo. Up to 20% of patients were unable to tolerate Tacrine because of cholinergic side effects, generally gastrointestinal distress. Asymptomatic, reversible elevations of serum transaminase levels caused by direct hepatotoxicity occurred in about 50% of patients.

Tacrine's development and approval process helped set standards for antedementia drug trials and focused attention on proper evaluation for dementia. It afforded hope to patients who had given up on the possibility of an effective therapy. The Tacrine experience proved that despite the potential for cholinergic and hepatic toxic effects, nonselective cholinergic therapies can be safe when used properly. Some patients who showed only mild improvement with tacrine therapy nonetheless viewed this as important, as did their caregivers. The tacrine experience

**Long-term cholinesterase therapy for Alzheimer's disease may retard cognitive deterioration over time, even in patients who fail to improve with short-term therapy.**

also facilitated the development of a host of other cholinesterase inhibitors. Further, recent evidence suggests that prolonged treatment with tacrine, in patients able to tolerate it, results in significant delay until nursing home placement.<sup>13</sup> These data are generally in agreement

with early long-term experience with other cholinesterase inhibitors. Finally, preliminary evidence suggests that tacrine, as well as other cholinergic agents, can produce positive behavioral effects?

**Second-generation cholinesterase inhibitors:**

Donepezil, formerly known as E2020, is a reversible acetylcholinesterase inhibitor that has dose-dependent activity showing greater selectivity for acetylcholinesterase and a longer duration of inhibitory action than tacrine or physostigmine, as well as greater.

**Table 2. Cholinergic therapies aimed at improving cognitive function in patients with Alzheimer's disease**

**Precursors**

Phosphatidylcholine (lecithin)  
Choline

**Cholinesterase inhibitors**

Tacrine HCl (Cognex)  
Donepezil HCl (Aricept)  
ENA 713 (Exelon)  
Metrifonate  
Eptastigmine  
Sustained-release physostigmine salicylate (Synapton)  
Galanthamine hydrobromide

**Cholinergic receptor agents**

Arecoline, pilocarpine HCl (Salagen),  
bethanecholchloride (Duvoid,  
Myotonachol, Urecholine), oxotremorine,  
nicotine Milameline AF102B SB202026  
Xanomeline

specificity for brain tissue than peripheral tissue. Encouraging preliminary studies led to the completion of multicenter, placebo-controlled studies examining donepezil at doses of 5 and 10 mg/day versus placebo for 15 and 30 weeks, respectively, as well as another 30-week trial conducted in Europe?<sup>15,16</sup> Results of these studies showed statistically significant benefit in

both of the primary outcome measures (cognitive function and global clinical impressions), which was somewhat greater at 10 mg/day. Donepezil has been reported to be safer and more tolerable (especially in terms of gastrointestinal distress) than tacrine. Donepezil was approved by the Food and Drug Administration (FDA) in November 1996 for a number of reasons: Its

efficacy is generally equivalent to that of tacrine, it is not associated with hepatotoxicity or elevated transaminase levels, and it is thought to have fewer cholinergic side effects than tacrine. The ease of its once-daily dosing may result in improved patient compliance. It also has reduced potential for drug-drug interactions and may be taken with food. Because of donepezil's improved tolerability and because therapeutic doses are achieved quickly, rather than taking months, substantially more patients are expected to experience benefit with donepezil than with tacrine.

Further information about donepezil also suggests that, as with some other cholinergic agents, improvement gained with early treatment is sustained with ongoing therapy? Studies are under way to assess donepezil's effectiveness over the long term as well as in patients with more severe dementia or comorbid medical conditions; results should help illuminate its usefulness in a broader patient population.

ENA 713 (Exelon) is a pseudo-irreversible cholinesterase inhibitor. Clinical trials in nearly 3,000 patients have been conducted, and details regarding efficacy and safety in these trials are likely to be available soon?

Metrifonate (originally developed as an insecticide) is an organophosphorous agent that does not inhibit cholinesterase but acts as a prodrug for the long-acting cholinesterase inhibitor dichlorvos.<sup>6</sup> The cholinesterase inhibition half-life is nearly 2 months, meaning that its effects are long-lasting. Early studies have shown significant improvements on both cognitive function and global clinical scales, accompanied by typical cholinergic side effects.

### **Cholinergic receptor agents:**

The rationale for the use of direct cholinergic agonists rests on the facts that postsynaptic muscarinic (m1) cholinergic receptors are relatively intact in Alzheimer's disease and that presynaptic m2 receptors, which are decreased in Alzheimer's patients, regulate acetyl-choline release. Although past trials of muscarinic cholinergic agents showed them to be minimally efficacious and to cause substantial side effects, newer agents now under development are expected to produce fewer toxic effects and to have greater affinity for the m1 and m2 receptors.<sup>4,5</sup>

Other neurotransmitter strategies: Disturbances of central catecholaminergic systems in Alzheimer's disease and the role of these systems in brain-related functions provide the rationale for pharmacologic enhancement strategies. Trials with precursors (metyrosine [Demser], levodopa [Dopar, Larodopa]) and agonists (eg, clonidine hydrochloride [Catapres], guanfacine hydrochloride [Tenex]) have shown largely negative results.<sup>3</sup>

Selegiline hydrochloride (Eldepryl) is a monoamine oxidase (MAO) inhibitor that relatively selectively inhibits MAO type B activity, thereby increasing dopamine and trace neurotransmitters such as phenylethylamine without substantially affecting norepinephrine levels.<sup>19</sup> A series of studies, ranging from several weeks to about 6 months in length, generally showed mild improvement in cognitive function in Alzheimer's patients who received, selegiline compared with those who received placebo.<sup>19</sup> Positive behavioral effects have also been reported.<sup>7</sup> In addition, selegiline has been evaluated in a 2-year, multicenter, placebo-controlled clinical trial; results are due out as this article goes to press.

Some medications intended to enhance serotonin function have shown significant behavioral and cognitive efficacy (eg, citalopram), while others have shown minimal or no behavioral or cognitive effects (eg, zimelidine, L-tryptophan [Trofan, Tryptacin], alaproclate)<sup>1,3</sup>

### **Enhance cerebral metabolism**

The finding in Alzheimer's patients of regional decreases in glucose utilization and abnormal oxidative metabolism has led to medication studies aimed at correcting these abnormalities.

#### **The finding of regional decreases in glucose utilization and abnormal oxidative metabolism in Alzheimer's patients has led to medication studies aimed at correcting these abnormalities.**

Ergoloid mesylates (Gerimal, Hydergine, Niloric) are among the most frequently prescribed medications in the world and have been used the longest as a putative cognition-enhancing therapy. Numerous clinical trials in mixed groups of elderly patients have not clarified their efficacy or clinical role, however.<sup>4,6</sup>

Nootropic medications are postulated to have a neuroprotective effect on the central nervous system against a variety of insults, although no specific mechanism of action relevant for dementia has been established for them. Clinical trials have shown largely negative results.<sup>3</sup>

### **Stabilize membranes**

A variety of agents that may affect cell membrane function (eg, altered membrane fluidity or cholesterol content) have been studied, including gangliosides and phosphatidylserine. On balance, these agents have proved disappointing.<sup>1</sup>

### **Enhance neuronal sprouting**

Disturbances in neurotropic factor physiology may lead to dysfunction of neuronal cells. Although there is no direct evidence supporting an involvement of nerve growth factor (NGF) in the pathogenesis of Alzheimer's disease, animal studies suggest that NGF administration may promote neuronal survival regardless of the cause of any damage. Because NGF does not penetrate the blood-brain barrier, it requires administration by intraventricular catheter and

pump for use of carrier molecules. A small number of patients have been treated with intrathecal NGF in Europe with limited success but with side effects not previously seen in humans? Other strategies being developed for delivery of growth factors include intraparenchymatous administration, tissue transplantation, and injection of genetically modified cells.

An inverse relationship has been reported between estrogen replacement therapy and duration of dementia, and preliminary trials suggest a cognition-enhancing effect of estrogens in patients with Alzheimer's disease and in normal postmenopausal women.<sup>21</sup> Further clinical trials are under way to assess the potential for estrogens to delay progression of dementia and to improve cognition in women with Alzheimer's disease, as well as the potential of conjugated estrogens to delay time of onset of Alzheimer's disease.

Finally, one of the many apparent facets of selegiline is the neurotropic potential of its parent compound. It is in part for this reason that a prolonged trial of transdermal selegiline (which optimizes the ratio of parent compound to metabolites) is being conducted in the United States.

### **Decrease neurotoxins**

Elevated levels of MAO-F which are found in patient with Alzheimer's disease might lead to elevated level of neurotoxins. Environmental exposure to a variety of toxins may also lead to neurotoxic by-products via oxidative biotransformation. In either case, long term inhibition of MAO-B with selegiline, which may have antineurotoxic potential,<sup>5,6</sup> could theoretically retard progression of illness through antitoxic mechanisms. Vitamin E is another potential antioxidant. Both selegiline and vitamin E are under active study.

### **Decrease excitatory amine acids**

The N-methyl-D-aspartate (NMDA) receptor, a glutamate receptor subtype, has important effects on learning and memory. There appears to be a decrease in cerebral cortical and

hippocampal NMDA receptors in Alzheimer's disease. Agents aimed at regulating NMDA receptor transmission are being developed in the hope that they may improve the memory of Alzheimer's patients.

### Decrease inflammation

Emerging evidence indicates overactivity of aspects of immune function in patients with Alzheimer's disease.<sup>22</sup> The potential role for anti-inflammatory agents was supported by retrospective chart reviews showing that patients with rheumatoid arthritis who received long-term anti-inflammatory therapy had a reduced likelihood of Alzheimer's disease compared with a control group without arthritis.<sup>22</sup> This was further supported by the positive results of a small placebo-controlled trial of indomethacin.<sup>22</sup> A prolonged multicenter trial of prednisone, 10 mg/day, is currently being conducted.

### Alter metabolism of key proteins

Therapies aimed at blocking the abnormal phosphorylation of tau proteins, which may play a pivotal role in Alzheimer's disease, are under development. Also contemplated are interventions intended to prevent amyloid disposition, perhaps by restoring the function of the peptide responsible for cleavage of the precursor protein. Another related strategy would be to reduce brain concentrations of apolipoprotein E-4, perhaps with cholesterol-lowering drugs.

### Summary and conclusion

Treatment of Alzheimer's disease has in the past been limited to empirical trials of psychotropics for relief of behavioral complications. At present, tacrine and donepezil are the only FDA-approved antidementia agents available. In the very near future, however, other cholinesterase inhibitors (eg, ENA 713, metrifonate, long-acting physostigmine) are expected to be approved for clinical use. The evidence at this

point suggests that they have modest but meaningful clinical effects and possible long-term benefits. Clinical use of the newer agents is likely to be influenced by their side-effect profiles, which consist largely of cholinergic effects, although without the hepatotoxic effects associated with tacrine.

To what extent these agents are accepted by patients and physicians remains to be seen. On the one hand, benefits are modest; on the other, these medications are increasingly safe. Continuing research is clarifying the role of cholinergic therapy in relieving behavioral symptoms, as well as the possible effects on rates of illness progression, institutionalization, and even mortality.

In the not-too-distant future, physicians can expect to see a variety of medications, now in early stages of development, that are intended to affect cholinergic systems in other ways. Further down the road, a host of mechanism-based therapeutic strategies, which hope to deal with the first cause of this devastating illness, will have been assessed in clinical trials.

This article and its tables are adapted, with permission, from Tariot and Schneider.<sup>5</sup>

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## Alzheimer's Disease

# Pharmacologic Treatment of Noncognitive Symptoms of Dementia

Karlsson I. Pharmacologic treatment of noncognitive symptoms of dementia.  
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**Cognitive deterioration in dementia includes many changes besides memory disturbances, including agitation, delusions, hallucinations, anxiety, irritability, and aggressiveness. Antipsychotic drugs are often used to control behavioral symptoms, but their benefits are limited. Depression, which is common in dementia, is often associated with anxiety. Selective serotonin reuptake inhibitors (SSRIs) improve mood and reduce anxiety while causing few side effects; they are also useful in managing irritability. Thus, the SSRIs should be considered the agents of choice for treating noncognitive symptoms associated with dementia. Neuroleptics should be used exclusively in patients with severe behavioral or psychotic symptoms, and only those agents without anticholinergic effects should be administered. Neuroleptics can be coadministered with SSRIs in patients who are extremely aggressive. Anxiolytics may also be effective for short-term use. Future studies of drugs to treat the noncognitive symptoms of dementia should be placebo controlled and should evaluate the effects of those drugs on cognitive function.**

## Non-cognitive symptoms in dementia

The cognitive deterioration associated with dementia includes many changes, of which memory disturbances are the most prominent (1). In addition to this cognitive deterioration, many other mental alterations are common. These include agitation, delusions, hallucinations, anxiety, irritability, and aggressiveness (2). During the course of a dementing disorder, most patients will exhibit behavioral symptoms (2).

In assessing a patient with behavioral symptoms that are commonly seen in persons with dementia, however, it should not be automatically assumed that such symptoms result from the patient's dementia. Delirium with an unrelated etiology can cause behavioral symptoms (3), including agitation and disruptive behavior. Drugs, brain damage that is unrelated to dementia, somatic disorders, and environmental factors can all induce delirium in susceptible individuals (3). Initiating treatment aimed at reducing the severity of delirium is important, because it will ameliorate behavioral symptoms and often improve cognitive function

(3). Management of delirium requires prompt recognition and treatment of the specific underlying etiology.

Prescription and over-the-counter drugs are often associated with global cognitive impairment in elderly persons (4), and superimposed delirium is a common consequence of drug treatment in demented persons (3, 5, 6). Drugs with anticholinergic effects are the most frequent cause of delirium, but it can also result from administration of neuroleptics,  $\beta$ -blockers, benzodiazepines, and sedative-hypnotics. Thus, avoidance of drugs that can induce delirium is a fundamental principle in the treatment of dementia.

Antipsychotic medications are frequently used to control the behavioral symptoms of dementia. However, despite 40 years of clinical experience, the scientific basis for their use is questionable. Most studies evaluating their efficacy have had an open-label design, while few comparative studies were placebo controlled (7). In a meta-analysis of the use of antipsychotic drugs to treat the symptoms of dementia by Schneider et al (7), the authors concluded that the effects of the various

different neuroleptic drugs did not differ significantly. Their therapeutic effects are limited and, of 100 treated patients, only 18 may have improved. The possibility that neuroleptic treatment can impair cognitive function in demented persons remains to be evaluated.

The use of various non-neuroleptic drugs in the management of the behavioral symptoms of dementia has been investigated. In a review by Schneider & Sobin (8), it was shown that, with the exception of studies involving citalopram, the few placebo-controlled studies that were conducted had small sample sizes and demonstrated no more than modest efficacy for the study medication. This lack of efficacy and concerns about adverse effects have encouraged the evaluation of new diagnostic and pharmacologic strategies.

### **Depressive symptoms in dementia**

*Incidence and diagnosis* -- Depression occurs in 10% to 15% of persons over the age of 65 (9) and in approximately three times as many elderly persons with dementia (10). Although different studies have reported various incidence statistics reflecting the lack of adequate diagnostic criteria, lowered mood seems to be one of the most common noncognitive symptoms of dementia, probably affecting one third of demented persons. Major depressive disorder represents only a fraction of this number (11).

However, as with delirium, it is important to realize that exogenous depression whose etiology is distinct from that of the dementing process can arise in patients with dementia (12). Certain physical conditions, such as lung and pancreatic carcinoma and thyroid and adrenal disease can precipitate depression, as can some drugs, including  $\beta$ -blockers, reserpine, steroids, and alpha-methyl dopa.

Depression in Alzheimer's disease (AD) and vascular dementia is mentioned in the DSM-III-R (13) and DSM-IV (1), but criteria based on analyses of actual patients is still lacking. Most evidence indicates that the clinical picture of

depression in elderly persons and persons with dementia tends to differ markedly from that of major depressive disorder and from depression as typically diagnosed in younger persons. The depressive state usually observed in old and demented patients is a long-standing, gradually progressive disorder. Criteria for dysthymia or the research diagnosis of minor depression included in DSM-IV describes depressive disorders with similar pictures, but are primarily not made for elderly demented. Thus, both for scientific and clinical purposes, there is a need for a full description of and criteria for diagnosing depression in persons with dementia and in the elderly.

Although depression in demented or nondemented elderly people should usually be regarded as separate disorders with distinct etiologies, these disorders share common symptoms and treatment strategies. According to some reports, depression sometimes precedes cognitive decline in persons with dementia (14).

*The pathophysiology of depression* -- Evidence suggests that depressive disorders are associated with focal disturbances in the brain. Reduced glucose utilization in the left frontal lobe was found by Baxter et al (15) and Martinot et al (16) in three different types of depression. Drevets et al (17) analyzed the regional blood flow in familial depressive diseases and found evidence of increased blood flow in the left frontal lobe. That study also suggested that a circuit involving the prefrontal cortex, amygdala, and related parts of the striatum, pallidum, and medial thalamus is involved in the functional neuroanatomy of depression. These results suggest that focal lesions affecting these areas may induce depressive states. It is probable that such areas can also be involved in degenerative changes in dementia, especially in vascular dementia.

There is also ample evidence that serotonin (5-HT) disturbances may induce depression. In a study of the monoamine precursors 5-hydroxytryptophan (5-HTP) and L-DOPA using positron emission tomography (PET). Agren et al (18) found evidence of an increased left

prefrontal utilization of 5-HTP. The investigators concluded that the data show an ( abnormality in serotonin function but did not exclude the possibility of serotonergic hypofunction in major depression. The reduced serotonin activity that is known to occur in AD may contribute to the high incidence of depression in patients with AD.

Thus, it appears that depression beginning in advanced age may be related to degenerative changes within the brain. It is plausible that the disorder inducing the changes responsible for cognitive decline can also cause depressive symptoms. Cognitive decline and depressive symptoms should therefore be regarded as symptoms of the same degenerative brain disorder.

### **Anxiety and depression**

Anxiety is one of the behavioral symptoms commonly seen in patients with dementia, and it can also be induced by depression. In a study at our institute, 65 demented patients with depression were rated with the GBS scale, which measures motor, intellectual, and emotional reduction and also evaluates six symptoms commonly observed in dementia. A principal component analysis showed that depression together with anxiety and panic constituted one factor, while factors such as emotional reduction and low motivation were not included. Anxiety and depression have previously been described as a continuum (19), a concept that is important for the formulation of treatment strategies.

### **Pharmacologic treatment of depression and anxiety in dementia**

Antidepressive therapy for persons with dementia has received comparatively little attention. Tricyclic antidepressants have anticholinergic effects, which may have implications for cognitive function in elderly and demented persons (5,20). Low doses reduce cognitive functions, whereas higher doses may induce confusion. Cardiotoxic properties pose

another problem. In a double-blind study conducted by Reiffier et al, both patients randomized to weekly clinic visits and those who received imipramine improved on measures of mood while active substance reduced cognition by the conclusion of the study (21).

Unlike tricyclic antidepressants, the selective serotonin reuptake inhibitors (SSRIs) have few anticholinergic effects. In a double-blind study, Nyth et al (22) investigated the effects of citalopram on elderly people, some of whom were demented. Although improvement in depression was observed, the effects were not significantly superior to placebo before six weeks; there was no difference in response between demented and nondemented patients. Cognitive improvement was noted in patients with depression alone and in those with depression and dementia.

Because anxiety and depression appear to represent different points along the same continuum, the rational treatment for anxiety should be the same as that for depression. Treatment with anxiolytics is efficient in the short term, but side effects (including reduced cognitive function) and a gradual decline in efficacy limit their long-term use (23). Colenda has reported success in treating agitated demented patients with buspirone (24).

In a few studies, antidepressants have been evaluated for their effects on anxiety in elderly and demented patients. Anxiety has been reduced in demented patients who received citalopram (25, 26). However, because the period of time necessary for a decrease in the level of anxiety is as long as the time needed to improve the typical patient's depressed mood, additional symptomatic treatment with benzodiazepines is sometimes needed at the beginning of therapy.

### **Effects of SSRIs on behavioral symptoms in dementia**

Irritability is common in dementia and sometimes leads to aggressiveness. These symptoms are probably the most problematic for the patient's family and caregivers. Citalopram

has reduced irritability in demented patients who show no evidence of depression (25-27). Similar results have been noted in a placebo-controlled study of fluvoxamine (28). Reduction in aggressiveness usually occurs quickly without delay, suggesting that serotonin activation results in a direct effect on irritability and aggressiveness.

### **Use of neuroleptics in dementia**

Two recent placebo-controlled studies of the effects of neuroleptic treatment in demented patients are noteworthy. Petri et al (29) reported marked effects on different behavioral variables and psychotic symptoms, while Barnes et al (30) found only small effects and concluded that neuroleptics have a limited therapeutic role in dementia. Nevertheless, the investigators reported that some patients seemed to derive great benefit from neuroleptic therapy (30). Those with severe behavioral symptoms responded better than those with milder symptoms.

The careful meta-analysis of the benefits of neuroleptic treatment in patients with dementia undertaken by Schneider et al (7) invites skepticism about the widespread use of neuroleptics, because it indicates that the benefits of such therapy are extremely limited. Positive effects following neuroleptic withdrawal in elderly nursing home residents suggests that neuroleptic therapy is often overused in this patient population (31). Neuroleptics should be used cautiously in patients with dementia, with careful attention to both symptomatic improvement and the development of adverse effects (12).

### **Treatment strategies and areas for future development**

The use of SSRIs in the treatment of the noncognitive symptoms of dementia seems to be a promising therapeutic strategy, and SSRIs should be considered the drugs of choice for managing such symptoms as depression,

anxiety, irritability, and aggressiveness. Neuroleptics should be used exclusively in patients with severe behavioral or psychotic symptoms and only drugs without anticholinergic effects should be administered. In patients who display severe aggressiveness, SSRIs can be combined with neuroleptics. Anxiolytics may be effective when used on a short-term basis.

To date, most of the studies that have evaluated the treatment of noncognitive symptoms in dementia have been inconclusive because of limitations in their design or small patient numbers. Future studies must be placebo controlled and include evaluations of the effect of the study drug on cognitive function. New agents with highly selective mechanisms of action may offer a more favorable risk:benefit ratio than many of the drugs in clinical use today: Future studies must also compare the efficacy of pharmacological treatment with environmental treatment strategies (12).

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# **$\beta$ -Amyloid and Treatment Opportunities for Alzheimer's Disease**

Marwan N. Sabbagh, Douglas Galasko, and Leon J. Thal

Department of Neurosciences, University of California-San Diego and the San Diego VAMC, San Diego, CA  
Address correspondence to: Marwan N. Sabbagh, M.D., Neurology Service (9127) San Diego VA Medical Center, 3350  
La Jolla Village Drive, San Diego, CA 92161

## **Summary**

**Proposed treatments of Alzheimer's disease (AD) are most likely to succeed if they are based on an understanding of the complex biology of AD and its effects on cognition. Treatments may target a single component of the complex pathology of AD with the hope that by affecting an individual component of AD pathology, the disease course can be affected. One such component is  $\beta$ -amyloid (A $\beta$ ), a feature of the senile plaque. A $\beta$  may be critical for inducing the pathology seen in AD. Accumulation of A $\beta$  may result in a cascade effect thereby allowing for intervention at multiple different points to slow disease progression. Treatment may be directed towards decreasing A $\beta$  production, increasing A $\beta$  removal, and decreasing A $\beta$  aggregation. Treatment may be directed more distally by modulating downstream events possibly due to A $\beta$  such as free radical toxicity, decreasing inflammation, preventing cell membrane damage, restoring calcium homeostasis, preventing excitotoxicity, and blocking the cellular response to injury by inhibiting neuronal apoptosis. This review underscores the complex biology of A $\beta$  specifically looking at the potential targets of therapeutics based on A $\beta$  biology.**

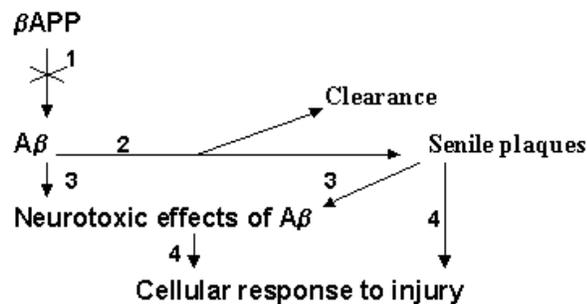
## **Introduction**

Alzheimer's disease (AD) is characterized by progressive loss of memory and orientation with preservation of motor, sensory, and linguistic abilities early in the disease. It evolves into global impairment that affects multiple cognitive domains [Friedland, 1993]. The gross pathology of the brain in AD is characterized by diffuse atrophy, especially of the cortex and hippocampus [Khachaturian, 1985]. Histologically, AD is characterized by neuronal loss in the nucleus basalis of Meynert, hippocampus, and association cortex; neuronal degeneration; dendritic pruning; synaptic loss; presence of neurofibrillary tangles (NFTs) containing paired helical filaments (PHFs) and the presence of senile plaques (SPs). Additional pathology includes granulovacuolar changes and accumulation of lipofuscin [Braak, 1994]. The SP of AD is a complex extracellular lesion composed of a central deposit of amyloid (the core) surrounded by activated microglia, fibrillary astrocytes and dystrophic neurites (dendrites and axonal terminals). The amyloid core consists of  $\beta$ -amyloid (A $\beta$ ), a predominantly 42kDa protein derived from its precursor amyloid precursor protein (bAPP) by proteolytic processing. It is produced by all cell types, and is not unique to neurons. Its aggregation and deposition in the brain, in both diffuse deposits and in amyloid cores in SPs is a defining lesion of AD.

A $\beta$  may be involved in the pathogenesis of AD. Views range from that of a causative agent to a secondary role as a marker of disease. Strong correlations between A $\beta$  load and the level of cognitive impairment are consistent with either claim [Cummings and Cotman, 1995]. Several lines of evidence suggest that A $\beta$  may play a key role in the pathogenesis of AD including in vitro evidence that A $\beta$  may be toxic to neurons and cultured cells, in vivo evidence for neuronal degeneration from exposure to A $\beta$ , and human genetic studies of early onset AD [reviewed in Selkoe, 1996]. Deposition of A $\beta$  may be an early and obligatory event in the pathogenesis of AD and evidence suggests that this deposition precedes the formation of tau-positive PHFs in NFTs [Duyckaerts et al., 1988] and is markedly accelerated in early onset inherited forms of AD.

Understanding the complex biology of AD and more specifically the biology of A $\beta$  and its parent  $\beta$ APP is a rational step in developing targeted therapeutics to arrest or reverse the progression of AD. Potential targets that will be discussed vis-a-vis the biology of amyloid are outlined in Fig. 1. This review will briefly discuss the biology of A $\beta$  and  $\beta$ APP and focus on its implications for therapy for AD.

**FIGURE 1: Potential Targets for Therapeutics in AD**



1. Decreasing A $\beta$  production by affecting  $\beta$ -APP processing
2. Preventing or reducing A $\beta$  aggregation and plaque maturation or improving clearance of A $\beta$  (e.g. through microglia or ApoE, ApoJ)
3. Inhibiting neurotoxic effects of A $\beta$  (e.g. restoring calcium homeostasis, reducing oxidative damage or decreasing inflammation)
4. Decreasing cellular response to injury

## Evidence from Human Studies for the Role of A $\beta$ in AD

Ab is produced and secreted as a soluble peptide during normal cellular metabolism in cultured cells as well as in humans. Secreted forms of bAPP and Ab can be detected in the brain and cerebrospinal fluid (CSF) of patients with AD and in normal individuals [Palmert et al., 1989, Haass et al., 1992a,

Shoji et al., 1992]. There are no known specific forms of Ab/bAPP unique to AD and the amount of bAPP or total Ab in the CSF has not been shown to correlate with the presence or severity of AD. Moreover, elevated total Ab levels in cultured fibroblasts and serum of AD patients occur only in early onset familial AD (FAD) and rarely in sporadic AD [Scheuner et al., 1996]. In order to incriminate Ab in the pathogenesis of AD *prima facie*, it is necessary to examine additional evidence from neuropathological, genetic and *in vivo* studies as summarized in Table 1.

**Table 1: Evidence from Human Studies for the Role of Aβ in AD**

- Deposition of Aβ defines AD and is an early event in AD
- Genetic forms of AD with early onset include deposition of Aβ at a young age
- Other neurodegenerative disorders (e.g. Huntington's disease, Pick's disease, PSP, etc.) do not lead to amyloid formation or Aβ deposition
- Levels of Aβ especially Aβ42 are markedly increased in AD brains
- Studies of serum and fibroblasts from patients with early onset FAD show increased production of Aβ or shifts favoring producing Aβ42 vs Aβ40 (Not for late onset AD)
- Mutations flanking the Aβ sequence in APP are associated with early onset AD
- Down's syndrome (trisomy 21) is associated with AD pathology

## Neuropathology

Aβ deposition in the core of SPs is an early and essential event regardless of age of onset of AD. The sequence of involvement of Aβ and other elements in plaque formation and the time required to generate them is not completely understood. The predominant element in senile plaque cores is Aβ, a ~4kD subunit protein that varies in length from 38 to 43 amino acids. This same peptide is central to the pathology of some forms of cerebral congophilic angiopathy [Rozemuller et al., 1993]. There are a host of other biochemical components of SPs including α1-antichymotrypsin (ACT), proteoglycans, and apolipoprotein E (ApoE) [Perlmutter et al., 1990, Fraser et al., 1993, Roher et al., 1993, Gearing et al., 1995].

Electron microscopy studies of AD cortex [Yamaguchi et al., 1988] have revealed innumerable, noncompacted deposits of Aβ ("diffuse" plaques) that contain few or no surrounding dystrophic neurites or glia. These deposits are not detected by Congo red, suggesting that there is a much greater amount of Aβ in AD brain than previously thought, including pre-amyloid plaques in brain regions that appear to be largely unaffected clinically (e.g., cerebellum and striatum) [Joachim et al., 1989]. Diffuse plaques are associated with aging, occur years before the onset of AD, and are found in clinically silent brain areas. This suggests that Aβ deposition alone may not be sufficient for the development of AD, and plaque maturation seems to be required. However, patients whose brains showed moderate amounts of diffuse plaques may have mild cognitive impairment ante-mortem suggesting that even diffuse plaques may be a possible correlate of impaired cognition [Morris et al. 1996]. Regardless of age at onset, which may range from 30 to 100 years of age, AD is always associated with Aβ deposition in the brain.

A $\beta$ 42 is the earliest species of A $\beta$  deposited. Shifts in the pathways that produce or remove A $\beta$ , especially forms of A $\beta$  ending at amino acid 42, may predispose to AD [Younkin, 1995]. Kinetic studies of aggregation of  $\beta$ 1-39,  $\beta$ 1-40,  $\beta$ 1-42 demonstrate that amyloid formation is a nucleation-dependent phenomenon, critically influenced by the length of the C-terminus [Jarrett et al., 1993]. A $\beta$ 40 is the predominant amyloid isoform found in CSF but is scarce in SPs, while the opposite is true for A $\beta$ 42 [Gravina et al., 1995, Motter et al., 1995]. Diffuse plaques, which may represent an early stage of A $\beta$  deposition, are almost exclusively A $\beta$ 42 [Iwatsubo et al., 1994]. Vascular amyloid seems to have predominantly A $\beta$ 40 [Gravina et al., 1995].

Amyloidogenesis may be promoted by the seeding of endogenous molecules such as proteoglycans or lipids that help to polymerize A $\beta$ 40 [Jarrett et al., 1993] and nucleation may be the rate-determining step of in vivo amyloidogenesis [Jarrett et al., 1993]. Abnormal C-terminal proteolysis could produce A $\beta$ 1-42(43) which in turn could seed aggregation of  $\beta$ 1-42 and  $\beta$ 1-40 [Jarrett and Lansbury, 1993], since  $\beta$ 1-40 readily forms amyloid fibrils with A $\beta$ 42 in vitro.

### Genetics

**Down's syndrome (i.e trisomy 21) leads to increased APP production.** The observation of AD changes in Down's syndrome (DS) brains led to the speculation that chromosome 21 was important in AD [reviewed in Tanzi, 1989]. Chromosome 21 is now known to be the locus of the gene for APP [Goldgaber et al., 1987]. DS patients have trisomy and thus an extra copy of chromosome 21. Therefore, they overproduce APP and A $\beta$ . Neuropathological studies have shown that A $\beta$  deposition occurs in DS at a very young age (20-30 years) [Wisniewski et al., 1985] and that the predominant species of A $\beta$  is A $\beta$ 42 [Teller et al., 1996].

**In FAD, APP mutations on chromosome 21 flank A $\beta$ .** Three different mutations at codon 717 of  $\beta$ APP have been reported [Yoshioka et al., 1991, Murrell et al., 1991, Chartier-Harlin et al., 1991] in families with early onset AD, which include conversion of valine to isoleucine, phenylalanine, or glycine. This mutation occurs just distal to the carboxyl terminus of the A $\beta$  domain. Shifts in A $\beta$  production favoring the release of A $\beta$ 42 occur in cell lines transfected with APP717 mutant DNA [Haass et al., 1995, Suzuki et al., 1994, Citron et al., 1994].

**In two large AD kindreds from Sweden, a tandem double mutation is linked to early onset AD.** This tandem double mutation affects codon 670 and 671 of the APP770 transcript in exon 16. Two base-pair transversions (G->T and A->C) result in lysine to asparagine and methionine to leucine amino acid substitutions [Mullan et al., 1992]. This tandem double mutation occurs just before the amino terminus of A $\beta$  within the APP protein and might interfere with proteolytic cleavage of APP at that locus. Increased production and secretion of A $\beta$  occurs in cell lines transfected with mutant Swedish APP [Citron et al., 1992].

**Presenilin mutations lead to amyloid deposition.** Chromosome 14 linkage has been reported in a number of autosomal dominant young onset pedigrees of FAD [St. George-Hyslop et al., 1992, Van Broeckhoven et al., 1992, Schellenberg et al., 1992] and may account for up to 50% of early onset cases. The chromosome 14 gene called S182, AD2, or presenilin 1 (PS-1) [Sherrington et al., 1995] encodes a predicted membrane-spanning protein [Doan et al., 1996] whose function and possible interactions with  $\beta$ APP are unclear. One theory relating chromosome 14 mutations and A $\beta$  is that the mutations may affect Golgi or membrane trafficking permitting  $\beta$ APP to stay in an amyloidogenic

## $\beta$ -amyloid and Treatment Opportunities

organelle longer, thereby enhancing A $\beta$  production [Selkoe, 1995]. Over 30 different missense mutations in the coding region of 10 exons of the PS1 gene have been identified in over forty families as well as one deletion mutation [Van Broeckhoven, 1995, ADCG, 1995, Kovacs et al., 1996].

Recently, the presenilin 2 (PS2; also called STM2) gene, on chromosome 1, which codes for a membrane protein with 70% amino acid sequence homology to PS-1, has been discovered to be linked to FAD [Rogaev, et al., 1995]. Two point mutations have been identified in families with PS2-associated AD [Levy-Lahad et al., 1995a, Levy-Lahad et al., 1995b].

Typically, PS1 mutations are associated with age of onset between 30 and 50, and PS2 mutations with age of onset between 50 and 70. Autopsy examination of individuals bearing these mutations show classic neuropathologic features of AD, namely SPs and NFTs. There is evidence that fibroblasts from patients with either PS1 or PS2 mutations show overproduction of longer forms of A $\beta$  [Scheuner et al., 1995], that plasma levels of A $\beta$ 42 are increased in these patients [Scheuner et al., 1996] and that cultured cells transfected with a variety of mutant presenilin genes show an increased ratio of A $\beta$ 42/40 [Borchelt et al., 1996]. Therefore, one of the effects of these mutations may be to increase secretion of A $\beta$ 42.

**Apo E may act via A $\beta$ .** Late onset FAD had been reported to be associated with a gene on chromosome 19 [Pericak-Vance, et al., 1991]. Within this genomic region is a gene for ApoE, encoding a 299 amino acid plasma protein [Ropers and Pericak-Vance, 1991, Weisgraber et al., 1994]. Two common polymorphisms exist, resulting in three isoforms, ApoE e2, e3, and e4. The most common isoform in the general population is ApoE3 [Mahley, 1988], secreted as a 299 amino acid protein having a single cysteine residue, at position 112. The other two common isoforms are ApoE2 (arginine at residue 158  $\rightarrow$  cysteine) and ApoE4 (cysteine at residue 112  $\rightarrow$  arginine) [Snipes et al., 1986]. Glu109 forms a salt bridge with Arg112 in ApoE4 but not with cys112 in ApoE3.

ApoE is found in the cytoplasm of neurons [Han et al., 1994a]. It regulates neurite outgrowth (isoform specific), and sprouting of dorsal root ganglia neurons in vitro [Handelmann et al., 1992, Holtzman et al., 1995], and appears to be involved in mobilization and redistribution of cholesterol in repair, growth, and maintenance of myelin and neuronal membranes during development or after injury [Mahley, 1988, Boyle, et al., 1989, LeBlanc and Poduslo, 1990].

The link between ApoE and AD pathogenesis is strong. In clinical series, the ApoE4 allele is overrepresented in late onset FAD [Strittmatter et al., 1993a] and cerebral amyloid angiopathy with hemorrhage [Greenberg et al., 1995]. The relationship of increased ApoE4 allele frequency in both sporadic late onset FAD patients has been extensively confirmed (e.g. Poirier et al., 1993, Corder et al., 1993, Mayeux et al., 1993, Saunders et al., 1993).

ApoE in CSF binds with high avidity to the A $\beta$  protein [Wisniewski et al., 1993, Strittmatter et al., 1993a] but CSF levels of total A $\beta$  appear to be independent of the ApoE genotype [Nitsch et al., 1995]. ApoE, along with amyloid P, glycosaminoglycans, and ACT may act as pathological chaperones that mediate  $\beta$ -pleated amyloid formation from A $\beta$ . ApoE is found in SPs, vascular amyloid and NFTs. A $\beta$ -apoE complexes have been purified from plaque cores. ApoE is also present in hippocampal neurons in AD even in the absence of NFTs [Han et al., 1994b].

The co-localization of ApoE with the major neuropathological features of AD plus the over-representation of the ApoE4 allele strongly suggests a role in the pathogenesis of AD.

Allele-specific functions of ApoE may contribute to the molecular mechanism of disease expression. Interactions between A $\beta$  and ApoE3 or E4 may affect amyloidosis. ApoE3 and transthyretin inhibit A $\beta$  aggregation in vitro by decreasing A $\beta$  multimers and inhibiting A $\beta$  nuclei formation [Schwarzman et al., 1995]. ApoE3 appears to be a more potent amyloid nucleation inhibitor in vitro than ApoE4 [Evans et al., 1995] and ApoE affects fibrillogenesis of A $\beta$ 1-40 in vitro [Castano et al., 1995]. ApoE4 may accelerate the rate of amyloid fibril formation (A $\beta$ 42 > A $\beta$ 40) more than ApoE3 or ApoE2 [Younkin, 1995]. ApoE4 homozygotes may have a reduced ability to suppress amyloid fibril formation in vivo. In vitro [Strittmatter et al., 1993b] and brain parenchyma studies have demonstrated an association between e4 allele frequency and increased A $\beta$  deposition [Schmechel et al., 1993, Gearing et al., 1996, reviewed in Selkoe, 1996]. Therefore, A $\beta$  may be a mediator of the increased risk of AD attributable to ApoE e4.

### **Evidence from In Vitro and Animal Studies for the Role of A $\beta$ in AD**

A direct link between  $\beta$ APP mutations and A $\beta$  overproduction has been established in vitro. Cells transfected with mutant APP 670/671 cDNA produce six- to eightfold more A $\beta$  peptide than cells expressing normal  $\beta$ APP [Citron et al., 1992, Cai et al., 1993]. However, cells transfected with the  $\beta$ APP construct with the valine to isoleucine codon 717 mutation did not show an increase in A $\beta$  production [Cai et al., 1993] but caused a selective increase in production of A $\beta$ 42 [Suzuki et al., 1994]. It is not clear how the various mutations result in  $\beta$ APP processing changes, but the common feature is a shift in the secretion of A $\beta$  that favors the formation of longer species of A $\beta$ , ending at position 42.

### **Table 2: Evidence From In Vitro and Animal Studies for A $\beta$ Playing a Role in AD.**

- A $\beta$  40 or A $\beta$  42 are cytotoxic to neuronal and other cells in tissue culture. This depends (among other factors) on the aggregation state of A $\beta$ .
- Under some conditions, A $\beta$  or aggregates of A $\beta$  may be neurotoxic when injected intracerebrally into animals.
- Transgenic mice overexpressing mutant forms of APP associated with early onset AD develop A $\beta$  deposition, neuritic pathology, and show behavioral changes. NFTs however, have not been seen.
- Transgenic mice over-expressing mutant presenilin genes associated with early onset AD show increases in the ratio of A $\beta$ 42/A $\beta$ 40 in brain tissue.

In situ evidence exists for possible toxic/neurodegenerative effects of A $\beta$ . Initial studies showed that injection of synthetic A $\beta$ 1-40 into the hippocampi of adult rats resulted in neuron loss 3 to 7 days after injection [Kowall et al., 1991]. These effects were blocked by preadministration of substance P. Subsequent studies showed that A $\beta$  injected into rat and monkey cerebral cortex produce greater neurotoxic effects than injection with control peptide [Kowall et al., 1992]. Tau-immunoreactivity is increased in tissue surrounding the A $\beta$  injections.

Not all laboratories have been able to confirm this work. One group injected human amyloid plaque

cores into the cortex and hippocampus of rats. Rats sacrificed up to one month showed little native amyloid plaque deposition or neuronal damage. Rather, the amyloid injected was phagocytized and cleared from the site of injection [Frautschy et al., 1992]. Chronic infusion of A $\beta$  intraventricularly did not lead to qualitative neuronal loss [Winkler et al., 1994]. Variability of results may depend on the vehicle used to solubilize A $\beta$  and the aggregation state of A $\beta$  [Waite et al., 1992]. Others have suggested that heparan sulfate proteoglycan may be an essential component needed for fibrillar A $\beta$  to evolve into plaques in cerebral cortex [Snow et al., 1994]. At present, the in vivo toxicity of A $\beta$  remains controversial.

The strongest in vivo evidence for the role of  $\beta$ APP and A $\beta$  in the pathogenesis of AD is the development of transgenic mouse models. The most convincing of these transgenic mice express high levels of human mutant APP with the 717 val-phe mutation [Games et al., 1995]. These mice progressively develop many pathological features of AD including A $\beta$  deposits, neuritic changes around these plaques, synaptic loss, astrogliosis, and microgliosis, but no NFTs [Games et al., 1995]. A second mouse model based on overexpression of the Swedish mutation of  $\beta$ APP demonstrates the presence of plaques, amyloid production, and age-dependent behavioral deficits in learning and retention [Hsiao et al., 1996]. These mouse models strongly support a primary role for  $\beta$ APP/A $\beta$  in AD. Additionally, they provide opportunities for screening new therapies, specifically those that may prevent conversion of soluble A $\beta$  to A $\beta$  deposits [Tanzi, 1995].

## **Biology of A $\beta$**

### **Mechanisms of Production and Depositon of A $\beta$ and APP**

The biology of APP and A $\beta$  has been extensively reviewed elsewhere [Younkin, 1995, Sisodia and Price, 1995, Ii, 1995, Selkoe '94, Selkoe, 1993, Mattson and Rydel, 1992b, Regland and Gottfries, 1992] and will only be summarized here. Understanding the processing and secretion of  $\beta$ APP and its relationship to A $\beta$  opens a window to target compounds aimed to prevent the accumulation of A $\beta$  by affecting the cleavage of APP, or the aggregation, clearance or toxicity of A $\beta$ .

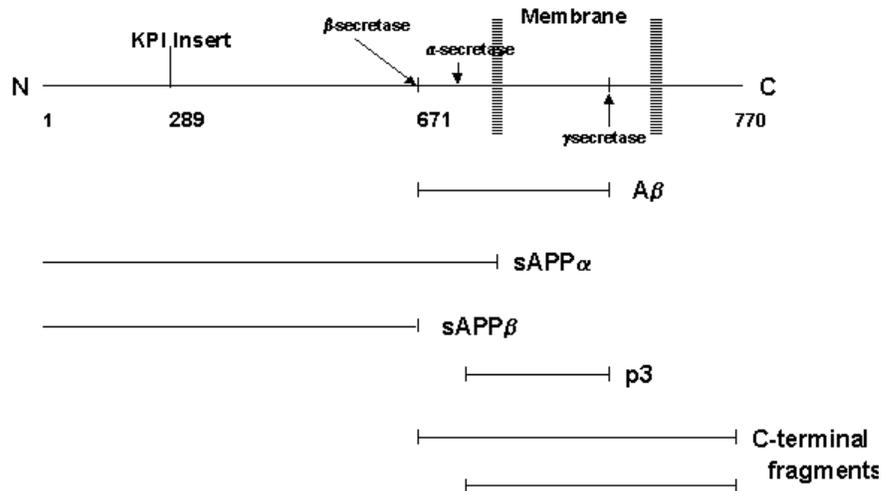
$\beta$ APP is a transmembrane glycoprotein with a large N-terminal region that can be secreted. The isoforms of APP, produced by alternate splicing, encode proteins each with a single membrane spanning region, a large extracytoplasmic region (ectodomain), and a small C-terminal intracytoplasmic region [Kang et al., 1987]. All of the  $\beta$ APPs are membrane-associated proteins that undergo N- and O-linked glycosylation, tyrosine sulfation, phosphorylation and proteolytic cleavage with secretion of the ectodomain [Weidemann et al., 1989, Oltersdorf et al., 1990, Schubert et al., 1988].

The most abundant isoforms in the brain are APP with 695 amino acid residues (APP695) (made up of exons 1-6, 9-18, not 13a), APP751 (exons 1-7, 9-18, not 13a), and APP770 (exons 1-18, not 13a) [Jacobsen et al., 1991, Johnson et al., 1990, Yoshikai et al., 1990]. APP751 and APP770 differ from APP695 in that they contain exon 7 which encodes a serine protease inhibitor of the Kunitz family. APP695 is the predominant form in neurons [Golde et al., 1990] where  $\beta$ APP is found on the cell surface and is anterogradely transported [Koo et al., 1990].

$\beta$ APP is processed by an exocytic (secretory) pathway, and an endocytic pathway. The exocytic pathway involves cleavage of mature,  $\beta$ APP at residue 687 of  $\beta$ APP770 between amino acid 16

(lysine) and 17 (leucine) of A $\beta$  by the protease  $\alpha$ -secretase (Fig. 2). Cleavage by  $\alpha$ -secretase occurs within the A $\beta$  peptide sequence, resulting in a secreted form of  $\beta$ APP (sAPP $\alpha$ ), a 10kD C-terminal membrane-bound fragment which is not amyloidogenic [Esch et al., 1990, Sisodia, 1992], and an additional 3 kD peptide (p3) which corresponds to a truncated fragment of A $\beta$  and other minor  $\beta$ -amyloid peptides [Haass et al., 1992a]. Cleavage by  $\alpha$ -secretase is not selective for APP and depends on the distance of the cleavage site from the membrane [Sisodia, 1992]. The p3 peptide is derived from the amino-terminal fragment of the 10 kD  $\beta$ APP carboxy-terminal peptide [Haass et al., 1993].

**FIG 2.: APP, Processing and Fragments**



The endocytic pathway involves reinternalization of mature  $\beta$ APP from the cell surface and targeting to lysosomes [Haass et al., 1992b] which yields a complex set of 8-12 kD carboxyl-terminal derivatives that include potentially amyloidogenic forms of the 4 kD A $\beta$  protein [Golde et al., 1992, Estus et al., 1992]. An acidic intracellular compartment other than lysosomes such as Golgi or early endosomes may be required [Haass et al., 1993].

Processing and secretion of A $\beta$  is thought to involve two cleavage steps that differ from APP processing by  $\alpha$ -secretase. The first cleavage occurs by  $\beta$ -secretase (thought to be intracellular, and associated with a post-Golgi compartment, possibly a late endosome) at Met671 of  $\beta$ APP creating a free amino terminus of A $\beta$  (ASP672). The second cleavage occurs at the C-terminal of A $\beta$  (A $\beta$ 40-43) by  $\gamma$ -secretase [reviewed in Selkoe, 1996].

Identification of these secretases has been elusive. The  $\gamma$ -secretase may be a member of the proteasome family that has chymotrypsin-like activity [Mundy, 1994], or there may be multiple  $\gamma$ -secretases. Recent data describes cathepsin D as a candidate APP  $\gamma$ -secretase [Evin et al., 1995].

## $\beta$ -amyloid and Treatment Opportunities

Others describe cathepsin S as the enzyme responsible for lysosomal processing of APP [Munger et al., 1995]. A $\beta$  can be produced from the A $\beta$ -bearing carboxyl-terminal  $\beta$ APP derivatives of the lysosomal pathway [Evin et al., 1995]. However, even in the presence of lysosomal inhibitors, cultured cells transfected with an APP construct containing the A $\beta$  sequence released significant amounts of a soluble A $\beta$  [Shoji et al., 1992].

Investigators have yet to determine the signal transduction mechanisms involved in  $\beta$ APP action. The normal biological role of APP and its secreted forms is unclear, and a receptor for APP has not been identified. Roles in adhesion (e.g. to laminin) have been suggested as well as roles as a neurotrophic factor or a transcytotic molecule. The biological functions suggested for  $\beta$ APP are summarized in Table 3.

### **Table 3: Biological Functions of Secreted $\beta$ -Amyloid Precursor Protein**

1. Growth regulation of fibroblasts
2. Promoting cellular adhesion
3. Affects synaptic plasticity and synaptic function; transcytotic
4. Protects against hypoglycemic damage
5. Protects against excitotoxicity
6. Promotes calcium homeostasis
7. Buffers copper and zinc ions

Processing and secretion of  $\beta$ APPs can be regulated by protein kinases, muscarinic receptor activity, and electrical activity [Mattson et al., 1993b, Caporaso et al., 1992, Nitsch et al., 1992].  $\beta$ APP expression is stimulated by endogenous factors such as cytokines, neurotrophic factors [Mattson et al., 1993a] such as basic fibroblast growth factors (bFGF) and epidermal growth factor (EGF) [Gray and Patel, 1993], and estrogens [Refolo et al., 1989, Schubert et al., 1989], or pathological conditions such as head trauma [Roberts et al., 1991], focal ischemia (expression of  $\beta$ APP with the Kunitz protease inhibitor) [Abe et al., 1991], and excitotoxicity [Siman et al., 1989].  $\beta$ APP expression is developmentally regulated. Increases in  $\beta$ APP occurs at the same time as neuronal differentiation [Fukuchi et al., 1992]. These and other factors could potentially influence A $\beta$  secretion and may be relevant to AD.

### **Evidence that A $\beta$ Production Leads to Neurotoxicity**

In vitro, A $\beta$  has either neurotrophic and neurotoxic effects depending on neuronal age, concentration of A $\beta$ , and whether fetal or adult neurons are examined [Yankner et al., 1990]. In its initial solubilized state, it may be neurite promoting and not toxic. Neurotrophic effects may reside in the first 28 residues of A $\beta$  since this fragment enhances neuronal survival [Whitson et al., 1989, Whitson et al., 1990]. A $\beta$  has also been shown to promote neurite outgrowth [Whitson et al., 1990, Koo et al., 1993] and stimulate neurotrophic factors [Araujo and Cotman, 1992].

Many mechanisms for the neurotoxic effect of A $\beta$  have been proposed (Table 4).

**Table 4. Proposed Mechanisms for Neurotoxicity of A $\beta$** 

1. Alteration of amyloidogenesis
2. Enhances vulnerability of neurons to excitotoxicity
3. Enhances vulnerability of neurons to hypoglycemic damage
4. Alterations of calcium homeostasis
5. Enhancement of oxidative damage
6. Activation of inflammatory pathways
7. Activation of microglia
8. Induction of lysosomal proteases
9. Alteration of tau phosphorylation
10. Induction of apoptosis
11. Damages membranes

The neurotoxicity of A $\beta$  is dependent on the length and aggregation state of A $\beta$ . In vitro aging of A $\beta$  causes neurotoxicity through peptide aggregation [Pike et al., 1991]. Fibrillar aggregates of A $\beta$  analogous to compact plaques were toxic to neurons in culture while amorphous A $\beta$  analogous to diffuse plaques was not [Lorenzo and Yankner, 1994]. This suggests that A $\beta$  neurotoxicity requires fibril formation. A $\beta$ 1-42 forms fibrillar aggregates far more readily than A $\beta$ 1-40 in vitro [Jarrett et al., 1993a] but once formed, aggregates of A $\beta$ 1-42 and A $\beta$ 1-40 appear to be equally neurotoxic [Pike et al., 1991].

It has been proposed that A $\beta$  causes little direct neurotoxicity by itself but enhances the vulnerability of neurons to excitotoxicity [Mattson et al., 1992] or hypoglycemic damage [Cheng and Mattson, 1992, Mattson and Rydel, 1992]. This may be mediated by increases in intracellular free calcium induced by A $\beta$  [Mattson et al., 1992]. Further studies confirm that the neurotoxicity of A $\beta$  is related to its aggregation state and age, and that A $\beta$  destabilizes neuronal calcium homeostasis [Mattson and Rydel, 1992]. A problem with most toxicity studies is that they use concentrations of A $\beta$  in excess of those found under physiological conditions; for example in CSF.

A $\beta$  deposition precedes formation of tau-positive PHFs of NFTs [Duyckaert et al., 1988, Mann, 1991]. The pathology of AD could be explained if A $\beta$  neurotoxicity triggers steps that lead to the formation of NFTs. However, there is little in vitro evidence for this. In one study, fetal rat hippocampal and human cortical neuronal cultures treated with fibrillar A $\beta$  showed marked induction of phosphorylation of tau, affecting its ability to bind microtubules [Busciglio et al., 1995], but the link between A $\beta$  and NFT formation has not been found.

A $\beta$  itself could promote toxic effects via several mechanisms. A $\beta$  may activate inflammatory pathways. Immunohistochemical studies have identified inflammatory cytokines such as IL-1 and IL-6, complement proteins such as C1q, C4 and C3, and acute phase proteins such as ACT in SPs [Rogers et al., 1992, Kalaria, 1993]. A $\beta$  stimulates microglial secretion of interleukin-1 (IL-1) and stimulates the proliferation of microglia in vitro [Araujo and Cotman, 1992]. Freshly prepared or aged A $\beta$  stimulate cytokine (IL-6 and IL-8) secretion [Gitter et al., 1995]. The addition of IL-1 augmented cytokine release in culture cells exposed to A $\beta$ , an effect that may depend on A $\beta$ 25-35 [Gitter et al., 1995]. Alternatively, microglial production of IL-1 may start a cascade of destruction by promoting expression of an astrocyte-derived cytokine which stimulates neurite outgrowth and increases intracellular free calcium levels [Mrak et al., 1995]. Additionally, IL-1 upregulates expression and

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processing of  $\beta$ APP and induces expression of  $\alpha$ -1-antichymotrypsin, thromboplastin and complement [Rogers et al., 1992, Mrak et al., 1995].  $A\beta$  and interferon  $\gamma$  (IFN $\gamma$ ) show synergism in triggering production of reactive nitrogen intermediates and tumor-necrosis factor- $\alpha$  from microglia [Meda et al., 1995]. Activation of microglia with IFN $\gamma$  and  $A\beta$  results in neuronal injury in vitro [Meda et al., 1995]. Thus, activation of several inflammatory pathways can lead to neurotoxicity.

Other factors found in plaques could cause a cascade of toxic effects to follow. For example, lysosomal hydrolases, normally an intracellular component, accumulate in SPs and increase as AD progresses [Cataldo et al., 1990, Cataldo et al., 1991]. At later stages of disease, large aggregates of hydrolase-positive lipofuscin fill the cytoplasm of neurons [Cataldo et al., 1994]. Following cell lysis, these aggregates are associated with deposits of  $A\beta$ . Activation of the lysosomal system may be an early and obligatory event for neuronal death in AD.

Yet another possibility is that  $A\beta$  is neurotoxic by enhancing oxidative metabolism [reviewed in Smith et al., 1995a].  $A\beta$  increases  $H_2O_2$  accumulation in cells, resulting in free radical-induced lipid peroxidation and cell death [Behl et al., 1994a]. This is thought to occur through activation of an NADPH-linked oxidase and may be a common oxidative mechanism among several amyloid diseases [Schubert et al., 1995]. Alternatively, free radical-induced cell death could occur through inhibition of 3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide (MTT), an enzyme involved in mitochondrial respiration [Hawtin et al., 1995, Shearman et al., 1994]. A third possibility is that free-radical cell death could occur through direct lipid membrane "shrapnel" damage.  $A\beta$  has been shown to fragment into free radical peptides in aqueous solution and the 25-35 fragment could conceivably be the fragment responsible for creation of reactive oxygen species [Hensley et al., 1994]. Further, the 25-35 fragment is a potent lipid peroxidation initiator in vitro which may in turn cause direct lipid membrane damage [Butterfield et al., 1994]. Amyloidogenic peptides such as  $A\beta_{40}$ ,  $\beta_2$  microglobulin, and human amylin increase reactive oxygen species (free radicals) as part of a cascade of neurotoxicity where induction of free radicals immediately precedes elevation of intracellular calcium concentrations [Mattson and Goodman, 1995]. A strong correlation exists between the intensity of free radical generation by  $A\beta$  and neurotoxicity [Harris et al., 1995]. Additionally, markers of oxidative metabolism such as zinc levels, iron content, and carbonyl-modified proteins are increased in AD brains while levels of free radical scavengers such as vitamin E are decreased in AD CSF [Tohgi et al., 1994, Smith and Perry, 1995, Smith et al., 1995b].

Finally,  $A\beta$  could be neurotoxic by inducing apoptosis. In vitro,  $A\beta_{42}$  is capable of inducing apoptosis in cultured cortical neurons [Forloni et al., 1993, Loo et al., 1993], an effect which could be blocked using a nuclease inhibitor [Cotman et al., 1994].  $A\beta$  may activate pathways leading to apoptosis through alterations of cellular calcium homeostasis or via increasing reactive oxygen species. Cortical cultures exposed to synthetic amyloid peptide exhibited morphological and biochemical characteristics of apoptosis [Loo et al., 1993] including membrane blebbing, compaction of nuclear chromatin and internucleosomal DNA fragmentation. A follow-up study using the 25-35 fragment of  $A\beta$  in cultured rat hippocampal neurons supported this finding [Watt et al., 1994]. Nevertheless, other results suggest that  $A\beta$ , specifically the  $A\beta_{25-35}$  fragment, induces necrosis rather than apoptosis as the final pathway of neuronal cell death [Behl et al., 1994b].

A number of enzymes and marker proteins have been identified that are involved in apoptosis including proteases of the interleukin-converting enzyme (ICE) family, ubiquitin and tissue transglutaminase [reviewed in Bredesen, 1995]. Experimentally, apoptosis in vitro can be precipitated by depriving neuronal cell lines of NGF and other growth factors [Haverkamp and Oppenheim, 1993].

Expression of the sulfated glycoprotein gene (sgp-2), a gene whose mRNA is expressed in increased levels (up to 1000-fold) during apoptosis in prostatic cells and lymphocytes is increased in AD [Duguid et al., 1989]. As another example, p75<sup>NTR</sup>, a proapoptotic gene enhances sensitivity to the toxicity of A $\beta$  when expressed in PC12 cells [Rabizadeh et al., 1994]. The extent to which apoptosis contributes to AD and is related to A $\beta$  deposition will require much further study.

### Opportunities for Treatment

Understanding the biology of bAPP and the mechanisms of the neurotoxicity of Ab allows for development of treatment strategies. Targets for several therapeutic strategies are outlined in Fig. 1 and specific options for treatment are summarized in Table 5.

#### Table 5. Potential Treatment Strategies

- Decreasing A $\beta$  production using secretase inhibitors to affect APP metabolism (increasing  $\alpha$ -secretase, decreasing  $\beta$  or  $\gamma$  secretase)
- Blocking A $\beta$  aggregation
- Prevention of amyloid fibril formation of A $\beta$
- Improving clearance of A $\beta$
- Blocking direct neurotoxic effects of A $\beta$  by restoring calcium homeostasis
- Preventing free radical toxicity
- Prevention of excitotoxicity
- Minimizing damage from inflammatory response
- Correction of copper and zinc imbalances
- Blocking the cellular response to injury by inhibiting neuronal apoptosis.

#### Decrease A $\beta$ Production

Identification of secretases related to APP could provide key targets of therapy. To prevent or decrease the release of Ab, one could either increase  $\alpha$ -secretase activity or decrease  $\beta$ - or  $\gamma$ -secretase activity. This is attractive from a therapeutic standpoint because intervention here affects a very early point in the cascade of events that leads to plaque formation and neuronal death. Despite significant progress in this regard, it is as yet unknown whether inhibiting intracellular processing enzymes can be accomplished safely.

Increase  $\alpha$ -secretase directly or indirectly (e.g. PKC or ACh). Activating  $\alpha$ -secretase might increase bAPP secretion, which may shift bAPP metabolism away from Ab production. Progress in this regard has been demonstrated in vitro. First, activation of intracellular protein kinase C (PKC) pathways with phorbol esters leads to an increase of  $\alpha$ -secretase cleavage of APP [reviewed in Gandy and Greengard, 1994]. Second, protein phosphatase inhibitors such as okadaic acid have also been shown to stimulate APP secretion in vitro [da Cruz e Silva et al., 1995]. Protein phosphatases are known to be highly expressed in neurons and glia of mammalian brain. Third, stimulation of the high affinity M1 muscarinic receptor subtype and the lower affinity M3 receptor subtype causes release of APP [Nitsch

et al., 1992]. Cholinesterase inhibitors, for example, have been shown to increase release of APPs in superfused rat cortical brain slices in situ [Giacobini, 1997]. If activating  $\alpha$ -secretase does decrease A $\beta$  release, then long-term cholinesterase treatment might slow the progression of AD. This has been explored in a follow-up study of long-term treatment with tacrine hydrochloride, which suggested but did not prove that patients exposed to treatment longest had a lower risk of institutionalization, a marker of AD progression [Knopman et al., 1996]. Fourth, manipulation of estrogens may affect APP secretion. Treatment in vitro with 17  $\beta$ -estradiol increases  $\beta$ APP [Jaffe et al., 1994]. Thus, affecting APP release might reduce the amount of A $\beta$  produced by neurons. Transgenic mice that overproduce A $\beta$  would be a good model to test the relevance of increasing  $\alpha$ -secretase activity.

Decrease  $\beta$  or  $\gamma$ ( $\beta$ 42g subtype) secretase activity or production. The  $\beta$ - or  $\gamma$ -secretases have not yet been identified and there is only indirect evidence of their subcellular localization. Pharmacological inhibitors of proteases are being used to gain clues to their identity and raise the possibility of selective inhibition of either of these secretases. The C-terminal glycosylated region of the secreted forms of  $\beta$ APP contains a proteinase inhibitor domain for the metalloproteinase gelatinase A. This gelatinase has secretase-like activity and may be involved in the formation of A $\beta$  [Miyazaki et al., 1993]. Follow-up studies of gelatinase A have suggested that it has  $\beta$ - rather than  $\alpha$ -secretase activity [LePage et al., 1995].

Bafilomycin A (baf A), a specific inhibitor of vacuolar H<sup>+</sup> ATPases, strongly inhibits release of A $\beta$  in a cultured of cell line transfected with the Swedish mutation of APP [Knops et al., 1995]. Unfortunately, this inhibition does not occur with wild type APP or with APPV717I, or in a neuroglioma-derived cell line. Another compound, the calpain inhibitor MDL 28170, has also been shown to reduce A $\beta$  production [Higaki et al., 1995] by stabilizing C-terminal fragments of APP that have already been cleaved by  $\gamma$ -secretase. Further analysis reveals that MDL 28170 selectively inhibits  $\gamma$ -secretase activity on A $\beta$ 40 rather than A $\beta$ 42 suggesting that there may be different  $\gamma$ -secretases for A $\beta$ 40 and A $\beta$ 42 [Citron et al., 1996]. This finding may have significant implications in developing compound that selectively affect A $\beta$ 42. Recently, agents such as as baf A1, brefeldin A, NH<sub>4</sub>Cl have been shown to decrease A $\beta$  production in several cell lines, presumably by inhibiting  $\beta$ -secretase or altering protein trafficking [Knops et al., 1995, Asami-Odaka et al., 1995].

It is not clear whether secretase inhibition will be a realistic form of therapy. Inhibition of  $\beta$ - or  $\gamma$ -secretase may be feasible without impairing cellular function if these secretases are A $\beta$  specific. Theoretically, inhibition of  $\beta$ - or  $\gamma$ -secretase may be highly desirable if there are different secretases for A $\beta$ 42 than A $\beta$ 40. However, the specificity of  $\gamma$ -secretase has been challenged recently [Tjernberg et al. 1997]. A critical consideration that may hamper realistic development of compounds targeted at secretases is that these enzymes may have other important biological roles besides APP cleavage. Many of these inhibitors may fail to cross the blood-brain barrier rendering them ineffective centrally. The  $\beta$ - and  $\gamma$ - secretases are intracellular and inhibitors will need to gain access to the subcellular locations of these enzymes. Thus, secretase inhibition may produce undesirable side effects and may have high toxicity.

### **Decrease A $\beta$ Aggregation or Deposition**

Synthetic peptides, antichaperone protein therapy, and glycosaminoglycans (GAGs). Decreasing the propensity of A $\beta$  to aggregate could have potential therapeutic benefits. This could be accomplished either through manipulation of pathological chaperones or inhibition of aggregation directly. Analysis of the "pathological chaperones" in plaques associated with A $\beta$ , including proteoglycan containing

GAGs, ACT, and possibly ApoE has been encouraging. In the rat PC12 cell line, GAGs are able to attenuate the neurotoxic effects of A $\beta$ 1-40 and A $\beta$ 25-35 as shown by decreased reduction of the dye MTT in vitro [Sadler et al., 1995, Pollack et al., 1995]. This suggests that GAGs may affect aggregation, and manipulation of GAGs could alter A $\beta$  deposition. ACT, another component of the SP also appears to affect the biology of A $\beta$ . When added in vitro, ACT inhibited A $\beta$  fibril formation [Ericksson et al., 1995]. Further, ACT promoted disaggregation of preformed A $\beta$  fibrils. Much further development will be required before these molecules (or analogs) could be considered for clinical testing.

Other types of molecules have been tried in efforts to inhibit A $\beta$  aggregation. Only those for which there are published data will be mentioned here. First, the antibiotic rifampicin, used in the treatment of tuberculosis and leprosy, inhibits aggregation and fibril formation of synthetic A $\beta$ 1-40 in vitro and prevents neurotoxicity in rat PC12 cells [Tomiyama et al., 1994]. Second, a synthetic peptide KLVFF, which is the A $\beta$ 16-20 sequence, can bind to full-length A $\beta$  and inhibit fibril formation in vitro [Tjernberg et al., 1996]. Third, antibodies to A $\beta$  [Solomon et al., 1996] can decrease A $\beta$  aggregation in vitro. Fourth, changes in cerebral zinc levels may affect A $\beta$  adhesiveness thus affecting fibril aggregation or catabolism [Bush et al., 1994]. Thus, manipulation based on factors associated with the SP could potentially suppress A $\beta$  deposition, and agents can be developed to inhibit aggregation. One problem to consider with all forms of treatment aimed at decreasing A $\beta$  aggregation is how to target the A $\beta$  monomers at widespread extracellular sites throughout the brain.

### **Increase Clearance of A $\beta$**

Enhancing degradation and clearance of A $\beta$  may be useful approaches to decreasing the amyloid burden. Degradation may be directly achieved by proteases or indirectly by enhancing cellular uptake of A $\beta$ . For example, a previously unidentified serine protease other than trypsin or chymotrypsin that complexes with alpha-2-macroglobulin has been shown to degrade A $\beta$  in vitro; this may be a normal mechanism of clearance [Qui et al., 1996].

The chemotherapeutic agent 4'-iodo-4'-deoxy-doxorubicin (IDOX) induces amyloid resorption in patients with immunoglobulin light chain amyloidosis. In vitro, IDOX binds strongly to all natural amyloid fibrils tested: immunoglobulin light chains, amyloid A, trans-thyretin, A $\beta$ , and  $\beta$ -2-microglobulin. IDOX inhibited amyloid fibrillogenesis and reduced formation of amyloid deposits, thus facilitating clearance of soluble amyloid [Merlini et al., 1995]. This approach is worth testing in model systems relevant to AD.

Clearance of A $\beta$  may be achieved by microglia or other cells. Microglia have been shown to remove A $\beta$  in vitro [Shafer et al., 1995] via receptor mediated pathways [Paresce et al., 1996]. However, the presence of GAGs and other proteoglycans appear to retard this effect [Shafer et al., 1995]. Activation of microglia may have the undesirable effect of attracting chemotactic and inflammatory molecules and producing toxins such as free radicals thereby worsening in situ damage.

Clearance of soluble A $\beta$  may be achieved by receptor-mediated internalization of carrier proteins. For example, A $\beta$  bound to ApoE or to lipoprotein particles would be available for uptake via receptors. An analogy would be the treatment of hypercholesterolemia by inducing receptors indirectly using 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMGCoA) reductase inhibitors. There are several receptors for ApoE in the brain [Rebeck et al., 1995] and they may prove to be a worthwhile target if ApoE-mediated cellular uptake of A $\beta$  is an important pathway in the brain.

### **Decrease Cellular Effects of Aβ Deposition**

Assuming that Aβ is a neurotoxin in AD allows several therapeutic directions to be explored. Major themes related to Aβ toxicity will be discussed.

**Restoration of Calcium Homeostasis.** Aβ may cause neurotoxicity through alteration of calcium homeostasis. In theory, restoration of calcium homeostasis should rescue neurons from the toxic effects of Aβ. This has been partially tested and the results are inconclusive. There are several lines of evidence supporting the importance of restoration of calcium homeostasis. First, voltage sensitive calcium channel blockers attenuate the toxic effects of Aβ in vitro [Weiss et al., 1994]. Second, hippocampal neurons expressing high amounts of calcium binding protein (i.e. calretinin) resist the neurotoxic effects of Aβ<sub>25-35</sub> and Aβ<sub>1-42</sub> [Pike and Cotman, 1995]. Third, selective depolymerization of actin microfilaments attenuates the calcium destabilizing toxicity of Aβ, suggesting a potential protective effect for microfilament depolymerizing compounds such as cytochalasin D [Furukawa and Mattson, 1995]. Thus, calcium homeostasis could be achieved through several routes.

On the other hand, other evidence fails to support the role of calcium in Aβ toxicity. First, when hippocampal neurons were exposed to Aβ<sub>1-40</sub>, calcium channel blockers such as ω-conotoxin, verapamil, and nifedipine did not attenuate neuronal death [Whitson and Appel, 1995]. Second, cyclic nucleotides such as dibutyryl cAMP, 8-bromo cAMP, dibutyryl cGMP, and 8-bromo cGMP also failed to alter Aβ toxicity. Third, colchicine, a microtubule disrupting agent did not exert a neuroprotective effect [Furukawa and Mattson, 1995] despite a well described therapeutic benefit in another amyloid-based disease, familial Mediterranean fever (FMF) [Livneh et al., 1994]. Fourth, clinical trials of nimodipine in AD did not slow disease progression [Grobe-Einsler and Traber, 1992, reviewed in Morich et al., 1996]. To date, available data does not support calcium channels and cyclic nucleotides as useful targets to prevent Aβ neurotoxicity.

Other drugs may indirectly influence intracellular calcium concentrations. For example, the anticonvulsants carbamazepine, phenytoin, and valproic acid protected rat hippocampal neuronal cultures from the neurotoxic effects of Aβ<sub>1-40</sub> by attenuating the elevation of intracellular free calcium concentration [Mark et al., 1995]. Further indirect support comes from the finding that GABAergic neurons are resistant to Aβ neurotoxicity [Pike and Cotman, 1993]. Additionally, anticonvulsants appear to suppress alterations in tau and ubiquitin immunoreactivities induced by exposure to excitotoxins [Mark et al., 1995].

**Modulate excitotoxicity.** Many studies have tried to alter the neurotoxic effects of Aβ by modulating potential excitotoxicity mediated by glutamate receptors. Hippocampal cultures exposed to Aβ<sub>1-40</sub> showed no attenuation of cell death in the presence of NMDA antagonists APV and MK801 [Whitson and Appel 1995]. In another study, Aβ<sub>25-35</sub>-induced apoptosis was insensitive to ionotropic glutamate receptor antagonists but was attenuated by the metabotropic glutamate receptor agonist (1S,3R)-1-aminocyclopentane-1,3,-dicarboxylic acid [Copani et al., 1995]. This may occur through the ability of metabotropic glutamate receptor agonists to decrease Ca<sup>2+</sup> membrane conductance.

Despite the mixed results regarding protection against excitotoxicity, NMDA and AMPA antagonists are under intense scrutiny as potential therapeutic agents in a variety of diseases such as stroke, Parkinson's disease and epilepsy [reviewed in Thomas, 1995, Doble, 1995, Hirose and Chan, 1993, Beal, 1992]. Clinical trials are underway testing NMDA antagonists in stroke [Bullock, 1995, Doble,

1995]. Milacemide, a glycine prodrug that exerts its effect through binding the AMPA receptor has been tried in the treatment of seizures, Parkinson's disease, Huntington's chorea and AD. Milacemide has been shown to enhance memory performance in control subjects [Schwartz et al., 1992]. However, two double-blind, placebo-controlled multicenter trials of Milacemide have failed to demonstrate any therapeutic benefit in the treatment of AD [Dysken et al., 1992, Cutler et al., 1993]. Though excitotoxicity is postulated to occur in AD, clinical trials using NMDA/AMPA antagonists for AD have not demonstrated benefit.

**Antioxidant therapy.** Altering the neurotoxic effects of A $\beta$  by modulating the oxidant effects of free radicals has been attempted in vitro. Addition of antioxidants such as propyl gallate, vitamin E and spin traps such as N-tert-butyl-alpha-phenylnitron attenuated neurotoxicity in cultured cells exposed to A $\beta$ 1-40 [Mattson and Goodman, 1995, Behl et al., 1992]. Furthermore, vitamin E promotes hippocampal neuronal survival in vitro and can restore hypofunctioning cholinergic neurons in rats [Nakajima et al., 1991, Maneesub et al., 1993]. In addition to A $\beta$  aggregation inhibition properties, the antibiotic rifampicin has shown promising free radical scavenging properties in vitro as well [Tomiyama et al., 1996].

Others dispute these findings. Acute exposure of rat hippocampal neurons to "aged" A $\beta$ 25-35 in the presence of inhibitors of nitric oxide, superoxide, and hydroxyl free radicals showed no demonstrable attenuation of neuronal loss [Lockhart et al., 1994]. Similarly, a reduction in free radical generation by selective inhibition of phospholipase-A2, cyclooxygenase, and lipoxygenase activities with quinacrine, indomethacin, and nor-dihydroguaiaretic acid (NDGA) did not reduce the effect of A $\beta$  inducing cell death [Lockhart et al., 1994]. Similarly, free radical scavengers vitamins E and C, glutathione, L-cysteine, N-acetyl-cysteine; and desferoxamine [Lockhart et al., 1994], failed to attenuate A $\beta$  neurotoxicity.

The antioxidant properties of L-deprenyl have been studied clinically in AD. Three trials have demonstrated slight improvement of neuropsychological parameters [Marin et al., 1995, Schneider et al., 1993, Tariot et al., 1987] but no effect on disease progression [Burke et al., 1993]. Results of a recent multicenter blinded, placebo-controlled trial of L-deprenyl and vitamin E in the treatment of AD demonstrate that both compounds slow the progression of the disease as measured by the primary endpoints of time to death, institutionalization or loss of activities of daily living (ADL) [Sano et al., 1997]. However, no demonstrable benefit on cognitive function was demonstrated by either drug in the trial. Lazabemide, another MAO-B inhibitor has also undergone clinical trials designed to alter the course of AD [Henriot et al., 1994]. Results have not yet been published. Acetyl-l-carnitine (ALCAR), which may augment the Krebs cycle and mitigate free radical damage appeared to slow disease progression in one trial [Spagnoli et al., 1991]. However, a larger follow-up trial was negative and disease progression was slower only in a subgroup of young onset rapidly progressing AD subjects [Thal et al., 1996].

**Decrease inflammation.** Another potential therapeutic option is to reduce the inflammatory response induced by A $\beta$  or Sps thereby decreasing neuronal injury. In addition to their effects on the lipo-oxygenase pathway, indomethacin and norhydroguaiaretic (NDGA) can inhibit IL-1 enhanced processing and secretion of APP [Dash and Moore, 1995]. Inhibition of the synthesis of inflammatory cytokines such as IL-1 and IL-6 as well as decreasing complement production may be useful therapies [reviewed in McGeer and McGeer, 1996a]. Alternatively, inhibiting the activation of microglia may be useful.

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The relationship between anti-inflammatory drugs and AD has been studied epidemiologically. Studies of patients with rheumatoid arthritis who take chronic doses of non-steroidal anti-inflammatory medication (NSAIDs) demonstrate a lower frequency of AD [McGeer et al., 1991], a finding confirmed in other epidemiological studies [reviewed in McGeer et al., 1996b]. Examination of a cohort with prospective collection of drug exposure data also corroborates the finding of a decreased incidence of AD in patients taking NSAIDs [Corrada et al., 1996]. One small clinical trial indicated less decline in a group of AD patients taking indomethacin than placebo over six months, but a high dropout rate complicates interpretation of this study [Rogers et al., 1993]. A double-blinded multicenter placebo-controlled trial of prednisone is in progress.

**Neurotrophic factors.** Neurotrophic factors are essential in neuronal development and maintenance. They can rescue neurons after axotomy and can attenuate the effects of toxic factors in vitro [Yuen and Mobley, 1996]. Consequently, they have been proposed as therapeutic agents for a variety of neurological conditions, including AD [reviewed in Yuen and Mobley, 1996]. Basic FGF (bFGF) prevents the neurotoxicity of A $\beta$  and the calcium destabilizing action of A $\beta$  in vitro [Mattson et al., 1993c]. Basic FGF is known to protect central neurons against EAA neurotoxicity and hypoglycemia [Mattson et al., 1993c]. Basic FGF is produced by astrocytes and neurons in vivo. Use of bFGF could provide yet another opportunity for therapeutic intervention by preventing the neurotoxic effects of A $\beta$ . However, this may be limited by the difficulty of delivering bFGF to the CNS since bFGF is not readily diffusible across the blood-brain barrier.

The use of NGF has been proposed in the treatment of AD. However success in the development of NGF therapeutically has been limited. NGF has not been found to have a significant effect on A $\beta$ -mediated neurotoxicity [Mattson et al., 1993c]. In rats, intraventricular NGF results in proliferation of Schwann cells around the brainstem [Winkler et al., 1997] suggesting that delivery of NGF will need to be site specific to limit untoward effects. The clinical administration of NGF via an intraventricular route has been attempted. NGF was administered to two patients with AD who experienced significant toxic side effects with no clear positive results [Olson, 1993]. The need to administer NGF by the intraventricular route limits its usefulness but has stimulated work designed to increase endogenous NGF by upregulating its message and transcription.

### **Affect Cellular Response to Injury (Including Apoptosis)**

In situ studies of brains from patients with AIDS and AD advance the apoptotic theory of cell death in these diseases. In one study, DNA fragmentation suggestive of apoptosis was increased 30 fold in neurons, oligodendrocytes, and microglia of AD brains [Lassman et al., 1995], while an immunohistochemical study of AD brain provides evidence of apoptosis in tangle-bearing neurons [Su et al., 1994]. Thus, apoptosis may serve as the final common pathway of cell death in AD [reviewed in Cotman and Anderson 1995], incited by a multiplicity of causes.

If apoptosis is the final common pathway of neuronal death, there may be opportunities to therapeutically intervene because a cascade of mediators, including proteases, and DNA-cleaving enzymes, play roles as activators or effectors of cell death. There are many soluble intracellular activators of apoptosis, including cysteine proteases related to ICE. It may be possible to selectively inhibit these activators, to decrease vulnerability to apoptosis. In tissue culture, use of agents such as NGF or free radical scavengers can decrease apoptosis. These strategies are far downstream in pathways that result in neuronal death or damage, and further basic scientific research is needed to define targets for intervention, to show whether they might be effective in acute or chronic situations.

## **Polypharmacy**

The mechanisms by which A $\beta$  exerts toxic effects have been treated individually above to illustrate reasonable targets for therapeutics. Aside from toxicity profiles, nothing precludes exploitation of these therapeutic targets in tandem or in concert. Certainly, most of the drugs mentioned are efficacious in vitro and are far from development clinically. However, some compounds are commercially available and could be used together. For example, cholinesterase inhibitors (tacrine and donepezil) which have symptomatic benefit and may affect APP secretion could be used with NSAIDs. Thus, A $\beta$  production and A $\beta$  neurotoxicity through pro-inflammatory cytokine production and microglial activation might be lessened simultaneously. Alternatively, anti-oxidants such as vitamin E or L-deprenyl could be used in concert with NSAIDs, affecting both free radical-induced lipid peroxidation induced by A $\beta$  and A $\beta$  neurotoxicity through pro-inflammatory cytokine production and microglial activation. The net effect of polypharmacy may result in synergism with greater symptomatic benefit or potential alteration of disease course.

## **Conclusions-How to Pursue Targets of Therapeutics**

The strengths of simple models, as well as their limitations and relevance to AD are important in interpreting early stages of drug development. For example, secretase function has been assessed indirectly, using cell lines that express (or overexpress) APP, and broad-spectrum pharmacological inhibitors. The identity of the secretases that control A $\beta$  formation needs to be established before the development of inhibitors can be optimized. A $\beta$  aggregation can be studied easily in vitro, although the conditions under which it is induced, the nature of the aggregates that form, and the concentrations that are used do not necessarily reflect the microenvironment of the brain where A $\beta$  is found in AD. Toxicity studies in non-neuronal cultures may not be relevant to AD, although they are convenient for drug screening. Cultured neuronal cells or organotypic brain slice cultures are likely to be systems closer to AD.

There is ample evidence to support the notion that A $\beta$  is necessary but may not be sufficient in producing AD pathology. Many mediators and mechanisms of cell death and neurodegeneration have been reviewed here which may be involved in neuronal death in AD. Each of these and other systems as well, have been proposed to be involved in the pathogenesis of AD. Evidence for many of these pathways is indirect, and pharmacological or biological evidence for intervention is usually based on in vitro models conducted under nonphysiological conditions. The greatest risk factor for the development of AD is age. Therefore, it is reasonable to hypothesize that additive and interactive effects of one or more of these mechanisms with the altered and declining function that occurs with normal aging, may be ultimately responsible for neurodegeneration in AD.

In pursuit of development of rational therapeutics for the treatment of AD, certain steps should be highlighted. First, simple but relevant basic models and strategies are needed to screen compounds. For example, identifying or purifying secretases to explore their pharmacology or to demonstrate a biological effect on amyloid production in cell culture would be a key step. In addition, several models are available including transfected cell lines to screen for A $\beta$  toxicity, or effects on APP processing, or A $\beta$  aggregation and clearance in vitro. Very simple models, such as A $\beta$  aggregation in vitro, while useful to define the kinetics of aggregation inhibitors, are not necessarily relevant to the brain. The conditions under which these models are tested should simulate the milieu of the brain, with realistic concentrations of reagents being used. Transgenic mice and cultured neurons or slices from these are useful models for longer-term studies of in vitro efficacy.

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Next, the pharmacokinetics of the compound must be considered. Questions such as distribution of the drug and its pharmacokinetics need to be evaluated. Gastrointestinal absorption and the ability to cross the blood brain barrier must be determined. The half-life of the drug should be measured and ideally it should be sufficiently long so that frequent dosing is not required. Ideally, oral administration should be possible, although alternative routes of administration might include the use of transdermal preparations or parenteral administration. The need for intracerebral or intrathecal administration would markedly dampen enthusiasm for the development and use of an anti-AD agent because of the surgical morbidity and technical problems associated with maintaining long-term pumps. Adequate toxicity studies of at least one year's duration as well as studies of mutagenicity will need to be carried out before human trials are initiated.

Molecules altering the deposition or enhancing the removal of amyloid may have one of two clinical effects. Such agents may be useful for slowing decline in individuals with clinical disease. Trials to demonstrate this mechanism of action will require the enrollment of several hundred subjects with early clinical AD, who are then followed for at least one year in order to determine whether or not the rate of decline on cognition, activities of daily living, and global functioning can be slowed. Conversely, compounds enhancing the removal of amyloid might be effective in delaying the onset of appearance of AD in a non-demented population. To test this approach would require the enrollment of a large number of subjects at risk for developing the disease. If a large enough population of individuals with known APP or presenilin mutations who are presymptomatic could be located, such subjects would be ideal for enrollment in a prevention trial. Given the rarity of these subjects, it is more likely that subjects at risk for developing AD would be enrolled in a trial designed to prevent normal individuals, or subjects with mild cognitive impairment, or people with one or two ApoE e4 alleles from developing clinically detectable AD.

Several years ago, there was clearly inadequate evidence to begin clinical trials of compounds designed to alter amyloid processing or deposition. The recent advances in our knowledge regarding the processing of APP and the more recent information linking the chromosome 1 and 14 mutations to an alteration in amyloid processing clearly lends sufficient weight to the underlying hypothesis that clinical trials of safe agents capable of altering amyloid deposition are now warranted, and may soon be feasible.

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## Alzheimer's Disease

# **Part 6**

## **Quality of Life**

## Alzheimer's Disease

# Quality of Life for Persons Living With Alzheimer's Disease: The Human Becoming Perspective

Rosemarie Rizzo Parse, RN; PhD; FAAN\*

**The purpose of this research was to ascertain the meaning of quality of life for persons living with Alzheimer's disease. The human becoming theory was the nursing perspective for this descriptive-exploratory study in which 25 people, designated as having mild to moderate Alzheimer's disease, were asked to describe their quality of life. Findings showed that quality for these participants is *a contentment with the remembered and now affiliations that arises amidst the tedium of the commonplace, as an easy-uneasy flow of transfiguring surfaces with liberating possibilities and confining constraints, while desiring cherished intimacies yields with inevitable distancing in the vicissitudes of life, as contemplating the ambiguity of the possibles emerges with yearning for successes in the moment. Implications for further research and practice are also discussed.***

Who can determine the quality of a person's life? Baltimore Orioles' shortstop Cal Ripkin Jr. created a new record on September 6, 1995, for the number of consecutive games played. The man whose record he broke was Lou Gehrig, first baseman of the New York Yankees, who was in the prime of his career when he was diagnosed with the debilitating neuromuscular disease that now bears his name. In a speech in Yankee Stadium in 1939, Gehrig said, "Fans, for the past two weeks you have been reading about a bad break I got. Yet today I consider myself the luckiest man on the face of the earth .... I might have had a bad break, but I have an awful lot to live for" (Robinson, 1990. pp. 263,264).

Who can determine the quality of a person's life? From the perspective of the human becoming theory, only the person's own description discloses his or her quality of life. Only the person there-living the life-can describe its quality (Parse, 1994b). This is true of those who have been designated by medical diagnoses as having some "cognitive impairment."

While little attention has been given to quality of life for special groups such as the elderly and disabled (Clark, 1988; Cohen, 1991; Dossa, 1989; Nickel et al., 1996), some research studies have been conducted in settings where the majority of clients have been considered to have some cognitive impairment (Aller & Coeling, 1993; Clark & Bowling, 1990; Cox, Kaeser, Montgomery, & Marion, 1991; Grant & Reimer, 1991; Keyer-Jones, 1990; Malott & McAiney, 1995; Minkler, 1981; Oleson, Heading, Shadick, & Bistodeau, 1994; Turner, 1993). For example, in one study in Ontario, Canada, experts including nurses, family caregivers, family physicians, psychiatrists, psychologists, and social workers were asked to

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*\*Loyola University Chicago*

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identify factors that they believed contributed to the quality of life of residents medically diagnosed with dementia (Malott & McAincy, 1995). The preliminary findings identified important factors related to quality of life for the resident, family, staff, and facility. The factors pertaining to residents were freedom from pain, low level of agitation, and ability to communicate needs in some manner. Family factors were quality of visits, family functioning, and knowledge about dementia; staff factors were desire to work with residents with dementia, knowledge about dementia, and specific skills training; and facility factors were commitment to quality, adequate number of staff, and special programs (Malott & McAincy, 1995, p. 12).

Another study by Oleson and colleagues (1994) compared perceptions of quality of life for ten residents and nine nursing staff of a long-stay institution in England, using a semi-structured interview approach. They found similar themes for both residents and nurses. According to these researchers, however, residents' perceptions tended to be more personal and were sometimes negative, whereas those of nurses tended to be more positive and were more reflective of professional duties. Aller and Coeling (1993) interviewed eight residents of a long-term care facility in Ohio, using a semi-structured format. They identified the following as influencing the residents' quality of life: (a) ability to communicate with other residents and staff within the facility, (b) ability to care for self, and (c) ability to help others.

Social psychology researchers with the Bradford Dementia Research Group in England, have described indicators of well-being which they conceptualize as quality of life in persons medically diagnosed with dementia, based on extensive observations. The 12 indicators of well-being were not written at the same level of discourse, making the findings difficult to interpret, but the significance of the findings is that they are based on the human actions and values as expressed by those observing the situation closely. Kitwood and Bredin also identified four global sentient states which these

indicators express: (a) sense of personal worth, (b) sense of agency, (c) social confidence, and (d) hope.

While these studies focused on quality of life with cognitively impaired persons, very little research has been done on the quality of life phenomenon from the perspective of persons designated as having Alzheimer's disease. And there have been only a few brief descriptive and personal accounts of this experience in the literature (Danforth, 1984; Winters-Miner, 1989). There are, however, a number of books written *communion-aloneness*. The third theme was *uncertain anticipation and confident knowing converge in understandings that fortify resolve for moving beyond*.

Mitchell and Jonas-Simpson (1995) conducted a study on quality of life framed by the human becoming theory (Parse, 1981, 1987, 1992, 1995) with 80 participants from the same chronic care facility as Mitchell's (1993) pilot study. The majority of the participants were over the age of 65, and some of them were medically diagnosed as having Alzheimer's disease or a related disorder. The first theme that emerged from the data was "treasured involvements with family and friends confirm a connectedness with the world" (Mitchell & Jonas-Simpson, 1995, p. 12). The second theme was "uplifting times of humor and genuine concern emerge with the suffering of disregard" (p. 25). The third theme was "shifting patterns of restriction-freedom reflect the struggle between wanting to care for self while having to rely on others" Findings from these two studies shed light on the meaning of quality of life as human becoming.

### Nursing Perspective

The nursing perspective from which this study emerged and through which the findings are interpreted is the human becoming theory (Parse, 1981, 1987, 1992, 1995), the principles of which are:

*1. Structuring meaning multidimensionally is cocreating reality through the languaging of valuing and imaging.*

## The Human Becoming Perspective

2. *Cocreating rhythmical patterns of relating* is living the paradoxical unity of revealing-concealing and enabling-limiting while connecting-separating.

3. *Cotranscending with the possibles* is powering unique ways of originating in the process of transforming.

This theory specifies that "one's lived experiences incarnate quality of life; thus, only the person living the life can describe it" (Parse, 1994). "Quality of life is the meaning one gives to one's life at the moment in cocreation with the universe". The meaning is what one chooses to attend to in the process of cocreating a personal reality. A description of quality of life as a personal reality discloses and hides all-at-once the connecting and separating with the universe of people, ideas, objects, and situations, which simultaneously enables and limits movement. In living quality of life, humans forge ahead and hold back in cocreating new ways of being like others yet unique, with the certainty and uncertainty inherent in choosing the changing of patterns of health.

### Research Question and Objectives

The research question of this descriptive-exploratory study was: What is the meaning of the experience of quality of life? The three objectives of the study with related interview questions were:

1. To describe the significance of quality of life.
  - a. What is life like for you?
  - b. What contributes to your quality of life?
  - c. What may diminish your quality of life?
  - d. What are your priorities right now?
2. To describe patterns of relating connected to quality of life.
  - a. Who is most important to you?
  - b. What changes in your routine or relationships

might change your quality of life?

3. To describe concerns, plans, hopes, and dreams related to quality of life.
  - a. How would you like to change your quality of life?
  - b. What can you do to make this happen?
  - c. What are your concerns?
  - d. What are your hopes and dreams?

### Participants and Setting

The participants of the study were 5 men and 20 women who were identified as persons who had been medically diagnosed with beginning or moderate Alzheimer's disease. This population is traditionally considered incompetent to give accurate information. From the human becoming perspective, however, all persons are considered able to share the meanings of their situations in some way. It was found that the participants in this study could talk about their quality of life. Sometimes their sentence structure was not clear and at times they did not complete a sentence, but the messages of their stories were clear as the interviewer spent time talking with them. Standard measures to protect the rights of participants approved by a human subjects' review board, were implemented. Most interviews took place in the private rooms of the participants at a multi-level care facility located in the midwest. Two interviews took place in the private homes of the participants.

### Data Gathering

Open-ended questions in relation to the objectives were used to begin discussions with participants. The interviewer sought depth and clarity through being sensitive to the flow of the conversation as guided by the descriptions given by the participants. Most interviews lasted 15-30 minutes. Discussions were tape recorded and transcribed.

### Data Analysis-Synthesis

Data analysis-synthesis was conducted according to the scientific process of the descriptive exploratory method (Parse, Coyne, & Smith, 1985). Transcripts were read and reread and major themes by objective were identified in the language of the participants. These themes were synthesized in the language of the researcher and the find-lags, the answer to the research question, were interpreted in light of the human becoming theory.

## Findings

The findings of this study are presented showing the themes in the language of the participants and the themes in the language of the researcher by objective with examples from the participants' descriptions that led to the cocreation of the themes.

### Objective 1: Meaning

#### Theme 1

*Language of Participants:* An appreciation of family and old and new friends resides along with living the humdrum routine day-to-day.

*Language of Researcher:* Contentment with the remembered and now affiliations arises amidst the tedium of the commonplace.

### Participant Statement

Day to day, life is average, nothing special, not as good as it used to be with family and friends. Friends of mine have all gone here, there, and everywhere. Well, I have a family yet. I have three, four [children]--I don't know anymore.... [I care] when it's something with my family. [One friend] calls me. then I do her, but she's that kind of person, kind of loyal. We've known one another since [I got married]. She lets me know she has been on a trip... and she will always send a card. And she is very good... and sometimes when I can't quite get the words out to her..., she knows that I have this..., but I don't care.

### Participant Statement

Life is fine. It's nothing very exciting, just

ordinary goings-on. Just to get along from day to day. I like to read, and go out and shop, and to go to the movies and theater. I don't go out too much, I'll be honest with you, but I do once in a while. It all sounds kind of dull, but it really isn't. And friends and relatives are still important, though I haven't too many relatives around anymore. [They contribute to my quality of life] just being there by me, I guess, somebody to talk with when you want to talk. Going to the theater used to mean going to the city, but there isn't much theater anymore.

### Participant Statement

Life is pretty dull now. I listen to the radio. I'm not with people very much. I still have a wonderful family, but they're all busy. Anything that I want to do is up to me to do it I don't enjoy much, to be very truthful. Just being with my children.

### Participant Statement

Life is humdrum, and exciting. It is quite different here-- different from home. We have a group of four or five young women, and they're called the Activities Committee. They plan all these things that they have an idea that we can do. It's the silliest thing you ever saw. It's a bunch of old ladies sitting in a circle on chairs, and we hardly ever get out of the chair. But... it's quite a workout and [we] enjoy it.... This is a great place. There's a lot of happy people here, and..., some develop friendships. You just talk with people, and you get so you laugh at the same things, and maybe discuss certain topics that you're both interested in. You just feel your way. Some develop friendships very quickly, and others are slower, and some people you rather dislike and avoid. It's just like it is anywhere.

### Objective 1: Meaning

#### Theme 2

*Language of Participants:* The smooth and troublesome straggles of change arise with opportunities and limitations.

*Language of Researcher:* The easy-uneasy

flow of transfiguring surfaces with liberating possibilities and confining constraints.

### **Participant Statement**

[Life] is not as good as it used to be. I have this illness now, and of course, I'm older, and that also doesn't help. The disease..., what I have that hasn't done much for me... because I can't do these things anymore .... I don't have [old] friends anymore..., and that makes a difference. Things have changed a lot ... but I do have family..., they're the only ones I have to go to, and yet, they get me mad at times. Oh, I just get kind of crabby, probably, and there are times I just get sick of it all. I hate to be this way with my family--- they can't do anything. (*Crying*). I don't earn my keep because I can't do that much anymore. I used to wash and iron, and everything, and now I don't really do that, and that makes a difference .... I used to do things around the house; I always liked to keep things in place, and now, I don't do much of that anymore. I used to like to talk, and these things have changed. When you talk to people sometimes... then..., you just can't..., and then you feel embarrassed..., people will watch you..., so enjoy life while you can. Yes, yes, enjoy! You don't know what's going to be knocking at your door, eventually. I never thought this would have [happened]. Naturally, when you get old, you get various problems, and things like that. But you never expect them to happen [to you]. If it's going to happen, it's going to happen to somebody else, not you .... I guess you think yours is the worst..., but I realize that there are a lot of people that have plenty [not just me].

### **Participant Statement**

The worst part is the eyesight. I don't know how I can improve my eyesight. It's gone. It's just old age, but that's my problem. Oh yes, I can hear; my hearing is going too, but I can still hear music. I enjoy music; otherwise there is nothing else to do. Of course, it's no good complaining, because there's nothing that nobody can do about it. I can't read the newspapers and see what's going on. So

basically, I'm in lousy, rotten shape. Because I used to enjoy reading the newspaper, and finding out the news. I can't do that; I can't see this damn TV .... But oh, in the summer, I wait for the summertime, out in the rose garden there. I always enjoy that, to go and sit out there when the sun is out, and it's beautiful. Oh yes, I can't wait to go outside.

### **Participant Statement**

So, my life has changed quite a bit now, because I'm here. This is one week only, and I'm finding out a lot of things. At first, it was a little hectic, and I didn't know what to do, but I got used to it, and I like it now. And the people here are nice to you, and you don't have to worry about if something goes wrong, or you get sick. They take care of you here, and that I like .... And I like it here. I was wondering if I would, but I'm satisfied .... It's better than being alone, like I was at home, in my own house. I was alone, and it wasn't good. I couldn't drive anymore, and I'd have to ask my neighbors all the time.

## **Objective 2: Rhythmicity**

### **Theme 3**

*Language of Participants:* Wishing for family closeness mingles with a general acceptance of being apart.

*Language of Researcher:* Desiring cherished intimacies yields with inevitable distancing in the vicissitudes of life.

### **Participant Statement**

So my family has to do all this stuff. Maybe to an extent. I wish I could do it again, and yes, I know, there's some things I could do better around the house, but I don't like it anymore. Who needs housework? That doesn't do anything [for me]; I've had a lifetime of that. Oh, maybe it was different because then many things were yours and many things were new. When I was a child, we had aunts, and uncles, and cousins, and things happened. It used to be fun, and now they're all gone. I don't have any family, except [our immediate family] here. Probably if I didn't have my family, I would be

in a real problem. Sometimes I wonder maybe it is easier going into a nursing home. Well, what happens happens!

### **Participant Statement**

I worship that son of mine. He's a bright boy, and he has gotten honors. He graduated from the military school, and he was very fortunate to have that. He's always been a joy to us. He is older now, that we can talk very frankly about things. He is living near--that's why I am here; he found this place. And now my son and his wife are going down to Florida. Well, I've had my time down in Florida; I've been down there a number of times, but they're not asking me to go, and I can understand why, because I'm an old person, and I wouldn't be doing all those things the youngsters do, you know; they're in swimming, and they're doing all those things that I would be, so I am happy about that.

### **Participant Statement**

I have twin daughters that live in California, and then I have two sons that live here. And they come to see me. Of course, the girls, I don't get to see very often, maybe once every two years or so. Their children all live in California, too, so I don't get to see them very often .... Of course, you know, with the boys, they don't have time. My oldest son took over our business after my husband retired. And then, my youngest son travels; he's not home very much. So I don't get to see them as often as I'd like, but then, after all, they have families too .... I'd leave the children, because they have their families and their children, and it isn't up to me to tell them what to do, so I just...they live their lives and I live mine.

### **Objective 3: Cotranscendence Theme 4**

*Language of Participants:* Considering the sureness-unsureness of what's next arises with wishes for simple immediate accomplishments.

*Language of Researcher:* Contemplating the ambiguity of the possibles emerges with yearning for successes in the moment

### **Participant Statement**

I wish this would all change, but it's not going to. Things have changed a lot, and I wish they would find something, a miracle thing, but that doesn't seem too likely. Oh, I'm sure some day they'll find out what to do. But after all, who am I when President Reagan, even if somebody such as he--so there's nothing much you can do .... Well, naturally, it would be better probably; I wish I could be out more..., just be outside.

### **Participant Statement**

I really love life, but I accept whatever is, for all of us. Right now, well, I'm in my 90s, and I expect that I'm not going to live a long time, but I'm not dwelling on it... and I will be--what-ever.

### **Participant Statement**

[What would change my quality of life is] just that I enjoy myself a little more. Get better acquainted here, and see my family more frequently. Just meeting people, I suppose. When you are new, it's difficult to meet up with different people, so that takes a little time. So far, [it's going] very nicely. For my future, I hope that everything goes well. Let's hope that I continue to function properly. And my dreams are of another world, I guess, when I'm long gone. When you pass away--whatever is ahead of you.

The findings of this study, then, are the themes arising from the descriptions of participants:

1. Contentment with the remembered and now affiliations arises amidst the tedium of the commonplace.
2. The easy-uneasy flow of transfiguring surfaces with liberating possibilities and confining constraints.
3. Desiring cherished intimacies yields with inevitable distancing in the vicissitudes of life.
4. Contemplating the ambiguity of the possibles emerges with yearning for successes in the moment.

The answer to the research question is: qua-

lity of life is *a contentment with the remembered and now affiliations that arises amidst the tedium of the commonplace, as an easy-uneasy flow of transfiguring surfaces with liberating possibilities and confining constraints, while desiring cherished intimacies yields with inevitable distancing in the vicissitudes of life, as contemplating the ambiguity of the possibles emerges with yearning for successes in the moment.*

## Discussion

Theme 1, *contentment with the remembered and now affiliations arises amidst the tedium of the commonplace*, surfaced in discussions with all participants as they talked about how their lives now compared to how they used to be. Their conversations reflected an appreciation for family and old and new friends as they described the humdrum of everyday by sharing the details about the unchanging routines. This theme was not apparent in the extant literature on quality of life in general nor in the research literature on quality of life for persons with cognitive impairment (Aller & Coeling, 1993; Clark & Bowling, 1990; Cox, Kaeser, Montgomery, & Marion, 1991; Grant & Reimer, 1991; Kayser-Jones, 1990; Malott & McAiney, 1995; Minkler, 1984; Oleson, Heading, Shadick, & Bistodeau, 1994; Turner, 1993).

Theme 2, *the easy-uneasy flow of transfiguring surfaces with liberating possibilities and confining constraints*, arose as participants spoke of the smooth and troublesome struggles in their changing patterns of living. They noted that there were many limitations in the now, but they hastened to add that opportunities were also present. Most participants could foresee gradual changes on the horizon, and, while most did not want to become dependent on others, they believed they would be safe. This theme indirectly reflected two global states (sense of personal worth and hope) of the four identified from the 12 indicators of well-being specified by Kitwood and Bredin (1992) as quality of life for persons medically diagnosed with dementia.

The participants in this study believed in themselves and, even with the troublesome struggles, could envision hope for the not-yet as they repeatedly pointed to other possibilities.

Theme 3, *desiring cherished intimacies yields with inevitable distancing in the vicissitudes of life*, emerged as participants spoke of wishing for family closeness yet gently accepting being apart. All participants spoke fondly of family relationships. Most wanted to see their relatives more often but recognized that their children, nieces, and nephews had lives of their own. This theme did not surface in the general literature on quality of life or in the literature on quality of life for persons medically diagnosed with dementia.

Theme 4, *contemplating the ambiguity of the possibles emerges with yearning for successes in the moment*, surfaced in participants' discussions when they thought about and considered what would be next in their lives. All participants said they knew they would change, yet were unsure of what would happen as they got older and wished for simple accomplishments in the immediate. This theme was not apparent in the general literature on quality of life but was alluded to in personal accounts of living with Alzheimer's disease (Danforth, 1984; Winters-Miner, 1989).

All four themes shed light on the meaning of quality of life in general and in particular for persons living with Alzheimer's disease.

The synthesized definition of quality of life arising from the descriptions of participants has four major paradoxical rhythms lived all-at-once as the was and will-be appear in the now. These rhythms are expressed at a higher level of abstraction and flow directly from the themes (see Table 1), surfacing in the context of contentment with the remembered and the now amidst the tedium of the commonplace. They are (a) calm-turbulence, (b) freedom-restriction, (c) certainty-uncertainty, and (d) togetherness-aloneness. These paradoxical rhythms of quality of life can be connected to the human becoming theory. The calm-turbulence rhythm of transfiguring arises with the shifting patterns of freedom-restriction amidst the certainty-

uncertainty of togetherness-aloneness.

These paradoxical rhythms are ways the human structures meaning, cocreates rhythmical patterns, and cotranscends with the possibles at many realms of the universe. The meaning of quality of life for the participants, who were designated as having beginning to moderate Alzheimer's disease, in this study was articulated in their stories of the ease and unease of change as new priorities were forged with deep appreciation for family closeness and friendships, even though the humdrum of the routine was ever-present with the lulls and agitations of ongoing change. The explicit knowings of their evolving situations were made clear in their descriptions of constraints in the now and the about-to-be. The constraints were discussed in light of new opportunities envisioned as participants were enabled and limited all-at-once. Some participants told of the stories of working, driving their cars, taking care of their homes, and helping others as they reflected on the changes in the now that restricted their movement.

The participants confirmed and did not confirm certain options as ways of changing. They spoke and were often silent in languaging their thoughts about the quality of their lives as they expressed concern about moving-being-still and about their patterns of relating with family and friends--telling some things and not others. Their attention to surroundings and activities is the way they connected and separated with their worlds, through the remembered, the anticipated, and the now all-at-once. They spoke about connecting and separating with events (exercise and shopping), ideas (reading books, watching TV), people (family and friends), and objects. The participants propelled their way through situations by pushing-resisting while creating new ways of becoming as they tried to conform yet not conform to what others desired. They wondered what was next as they contemplated what might happen to them, yet simultaneously they focused on cherished immediate successes and said they were ready for what might happen as the unfamiliar gradually changed to the familiar.

Quality of life for the participants in this study is incarnated in the calm-turbulent flow of the day-to-day as changing priorities cocreate different ultimate meanings in life while anticipated freedoms and restrictions arise in the moments of being together with and apart from others. Quality of life is inextricably woven with the certain and uncertain possibles that lie ahead--the not knowings of what is really next lingers with the knowings embedded in plans for the next day, the next meeting with family, or the next call from a friend.

### **Connection With Human Becoming Literature**

Three of the four rhythms arising from the themes in the descriptions of participants in this study are consistent with findings in the two other descriptive exploratory studies on quality of life guided by the human becoming theory with persons designated as living with Alzheimer's disease and related disorders (Mitchell, 1993; Mitchell & Jonas-Simpson, 1995). These are togetherness-aloneness, freedom-restriction, and calm-turbulence. Participants in all three studies in some way made explicit the closeness and distance with family and friends, the opportunities and constraints in transfiguring, and the ups and downs in the humdrum of the commonplace. The one rhythm, certainty-uncertainty, found in the present study is also explicit in the Mitchell (1993) study; participants in these two studies spoke of anticipated uncertainties simultaneously with confident knowings. All four paradoxical rhythms were also somewhat consistent implicitly with some of the non-research-based personal accounts of persons living with Alzheimer's disease reported in the extant literature (Danforth, 1984; Winters-Miner, 1989). The paradoxical rhythm of restriction-free-dom was the phenomenon of interest in a Parse research method study with 12 persons between

**Table 1**  
**Paradoxical Rhythms Emerging From the Themes**

Themes (participants' language)	Smooth-troublesome -	Opportunities-limitations -	Sureness-unsureness -	Close to-apart from -
Themes (researcher's language)	Easy-uneasy -	Liberating possibilities- confining constraints -	Ambiguity -	Intimacy -distancing -
Paradoxical rhythms aleness at the theoretical level	Calm-turbulence	Freedom-restriction	Certainty-uncertainty	Togetherness-

75 and 92 years of age conducted by Mitchell (1995). The structure of the lived experience of restriction-freedom was found to be "anticipating limitations with unencumbered self-direction while yielding to change fortifies resolve for moving beyond" (p. 175). The descriptions by participants from Mitchell's (1995) study are consistent with those descriptions that led to the identification of freedom-restriction in the present study. The participants, who were generally in the same age range in both studies, recognized their constraints yet envisioned other possibilities. Participants in both studies offered descriptions that reflected yielding to change yet moving beyond with the small successes in the now. The ideas of freedom-restriction and calm-turbulence were also found in the structure of the lived experience of struggling through a difficult time, a study conducted by Smith (1990) with unemployed persons. The structure stated that "struggling through a difficult time was sculpting new lifeways in turbulent change through affirming self while feeling expanded by assets and restricted by obstacles in the midst of grieving the loss of what was cherished." The paradoxical rhythm of togetherness-aloneness is one that has surfaced in several studies guided by the human becoming theory. The phenomena of concern in these studies were grieving (Cody, 1991, 1995; Pilkington, 1993), suffering (Daly, 1995), retirement (Davis & Cannava, 1995), and laughing and health (Parse, 1994a). In all of

these studies participants in some way made explicit the importance of being with and apart from others.

Clearly, the paradoxical rhythms found in the present study on quality of life are present in other lived experiences as evidenced in these research findings. As more research is conducted on various lived experiences and on quality of life, some synthesis of findings will be necessary to shed light on quality of life as the human's lived experiences of health at the moment (Parse 1994b).

## Conclusion

Persons designated as having beginning to moderate levels of Alzheimer's disease described the quality of their lives with much detail, and while at times they had difficulty getting words together in a sentence, they did tell their stories. The themes and four emergent paradoxical rhythms from this study provide the world of science with new knowledge about quality of life for persons living with Alzheimer's disease and about quality of life in general.

The new knowledge enhances the human becoming nursing theory by enriching understanding of human experiences and it adds substantial information to the extant general literature on quality of life which to date does not reflect these ideas. The findings from this study along with those from the Mitchell (1993)

and the Mitchell and Jonas-Simpson (1995) studies begin to build a substantive human science knowledge base about quality of life which sheds light on unitary human becoming different from the particulate perspective that now dominates the literature on this phenomenon. The new knowledge connected to the human becoming theory offers nurses a broader base from which to guide their practice. Knowing about the themes and paradoxical rhythms will guide the nurse as s/he moves with the rhythms of persons and families as they tell of their experiences, hopes, and dreams. Further research on quality of life from the human becoming perspective is necessary since the goal of nursing from this view is quality of life. Each one of the paradoxical rhythms uncovered in this study could be investigated further and then examined in light of the findings from other studies guided by the human becoming theory.

Dimsdale and Baum (1995) in their work "Quality of Life in Behavioral Medicine Research ask. "Is there a why of quantifying quality of life?" and "Is consensus possible about how to define quality of life?" And, this author asks, Who can describe the quality of a person's life? Who? The answer is--only the person living the life.

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## Alzheimer's Disease

## Pretending: A Way to Get Through the Day

Gail J. Mitchell, RN; PhD\*

*The days go by and I find I'm just drifting along. And then, I find myself in a different place and I know I must be kind of dreaming, but I am not really sleeping. Maybe I go to other places because it takes me away from here--from what I have become. I often think of days when I held my babies and I can smell them again and touch them and love them. I go to my father's dentist chair. I used to help him when I was a little girl. I really loved my father. I don't think my pretending hurts anybody, and, you know, I think it helps me get through the day.*

Mrs. J sits in her wheelchair and tells me about her pretending. It touches me in a profound kind of way as I watch this elderly woman's eyes fill with tears as she cradles her arms and once again rocks the infant who is them, yet not there. I embrace the moment of tenderness and joy that I am witnessing and I know in some way Mrs. J is cotranscending with the possibles of her universe. I am humbled and filled with wonder.

Mrs. J was diagnosed with Alzheimer's disease a year ago and she now lives in a chronic care hospital. For many nurses, who look at her and see a diagnosis first, Mrs. J is confused and disoriented. Care providers try to help Mrs. J by describing the reality they know. This is a hospital, in Canada, in February, on Tuesday. "IT IS WIN-TER TIME"; they tell her. She does not acknowledge their loudly spoken, well-intentioned words. No one stops to listen to

Mrs. J as she speaks of her experience with her father and children. She holds her arms out as if gathering someone close to her. Nurses walk by without recognizing her gestures or words. On occasion a staff member will ask Mrs. J if she wants a drink or if she is ready to go back to bed. Later, Mrs. J looks startled as they whisk her down the hall toward room 441, bed 3. Another day.

There is a yawning gulf in the realities described above, a gulf that holds important opportunities and limitations for nurses and for persons like Mrs. J who dwell in different realities, all at once. Many older people speak of pretending as a way to get through the day. Parse, Coyne, and Smith (1985) were the first to report this phenomenon, as a particular way to get through the day. In their study on the experience of aging, elderly persons spoke of pretending. One woman said:

*Pretending you're still at home keeps you from thinking about your family putting you here... not wanting you...it makes it easier to get through the day because..., you can be happy... and maybe...not so mad...you pretend you're a young woman again...getting the supper ready...you're not so lonesome...if you can remember all that..., well..., maybe..., maybe you won't go... senile. (Parse et al., 1985, p. 85)*

The practice approach nurses have with persons who rely on pretending to get through the day is all important issue to explore from different perspectives. The most prevalent nursing approach, described above as attempting to orient persons, has certain consequences that may actually expand the gulf between nurses and those they care for. At the very least one might expect that reality orientation isolates

\*Sunnybrook Health Science Centre;  
University of Toronto, Ontario, Canada

nurses and those who are nursed. A question that now awaits an answer is this: If nurses have practice options that might diminish this gulf so that patients/families experience a genuine respect, a true presence, will they choose to engage and honor the different realities experienced by persons?

If nurses believe that people know their own way, if nurses trust that people know what is helpful and what is not, as is suggested in the human becoming theory (Parse, 1981, 1992, 1995), then practice with persons who choose pretending as a meaningful experience holds new possibility. Parse's theoretical, principles and concepts present a nursing framework for understanding the phenomenon of pretending. Mrs. J clearly expressed her values, for the relationships she lived with her children and her father, and imaging the special people in her life represented her reality as experienced in the moment.

Nurses who are open to moments of joy, like that languaged by Mrs. J as she cradled her children, show an unconditional regard for the person's experience -- a moment that is transcendent for both participants in the nurse-person process.

To appreciate the pretending experience in a new way, nurses guided by Parse's theory also consider the enabling-limiting consequences that surface with every choice to live in a certain way. Pretending can be viewed as a way of connecting-separating with other people and other times. Expressions of the realities experienced when pretending signify the ways persons reveal and conceal their multidimensional realms of relating. Mrs. J, like other

persons, indicated that pretending is helpful. Perhaps it is a way of creating opportunities to leave a place of suffering or loneliness. The ways nurses attend to persons during times of pretending will enhance or diminish the possibilities that are not yet apparent. Respect and unconditional regard for another's experience are created in the intention of true presence.

Parse's theory helps nurses understand that human beings continuously transform toward greater diversity and new possibilities. Powering is recognized in the ways people move beyond the now moment and in the energy shown when cotranscending with the possibles. Mrs. J described her changing reality and her choice to drift to different places, to places that held joy and love. And nurses can now choose how they will view pretending. To honor another's reality is a choice that conveys respect for the mystery of being human. Rilke said, "The world is large, but in us it is deep as the sea" (Bachelard, 1994, p. 183). It is the depth of human experience that awaits nurses' knowing.

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# Quality-of-Life Issues in Home Care

BY SARAH B. KEATING

Home care services are often the preferred alternative, to institutionalization for the elderly person with chronic debilitating health problems or an acute episode of illness. Remaining in one's familiar home surroundings and having close family members at hand is generally considered most desirable. Nurses in home care, who have a focus on the family as well as the individual, can help the family to realistically assess the effects of home care on their quality of life. This includes an assessment of the ability to care for the family member at home, the effect on other household members' health, and the costs of providing home care. The following discussion reviews quality-of-life issues in home care.

## **The Patient**

A holistic approach to assess the patient's suitability to remain at home helps to determine the quality of his or her life at home. Physiologic assessment includes a complete health history and physical examination. What are the major health problems, including the medical and nursing diagnoses? If this is an acute episode of illness, is it expected that the client will recover more rapidly at home than in an acute care or extended care facility? If the health problem is chronic, will the client fare better at home with periodic visits from professionals and continuous care by the family member than in a skilled nursing facility? Or is the chronic disease rapidly deteriorating into a condition that will necessitate more intense care in a supervised

SARAH B. KEATING, RN, EdD, FAAN, is interim associate dean of the College of Health and Human Services. San Francisco State University.

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facility? To what extent may pain be controlled at home using noninvasive and invasive techniques? What are the safety hazards in the home? Is the location of the focus of care for the patient safe and accessible?

Much determines quality of life of a patient who is cared for at home. A client who feels safe and loved at home may well recover from an acute episode of illness more rapidly than in a health care facility. Institutionalization often causes depression, disorientation, and a sense of isolation from familiar surroundings and loved ones. It fosters dependence on health care providers, and the client often succumbs to the sick role and a feeling of helplessness. elders with mild dementia may function well in the familiar home environment but show marked impairment elsewhere.

***Remaining in one's familiar home surroundings and having close family members at hand is generally considered most desirable.***

Sociologic factors better met at home include cultural and ethnic health care beliefs, nutritional practices, religious and spiritual values, and economics. Staying at home maintains the elder's network of friends and contacts in the neighborhood and among family members. This is in contrast to a potential sense of isolation in an institution. Owing to geographic location costs and transportation limitations, elders are often in health care

facilities far from the family home. This situation prevents frequent visits from family and friends. Many elders still believe that admission to a nursing home signifies the last step before dying, even though rehabilitation institutions typically provide intensive therapies for persons recovering from strokes, injuries, hip replacements, cardiovascular problems, and so forth.

These facilities often provide the midlevel of care before the patient is discharged home. Various cultures and ethnic groups hold particular beliefs about where health care services should be provided. There are some cultures in which it is preferred that a family member die in an institution. Thus, hospice services provided in an institutional setting may be preferred to receiving services at home. In many cultures, the scientific, technical care available at an institution is thought to be desirable. People of such cultures believe that they will have more direct access to good medical care if they are in an acute care facility. Others prefer home care surrounded by loved ones and the knowledge that they have control of the services provided.

Religious and spiritual beliefs are often culturally based and vary widely. For many clients and their families, it is comforting to stay home for spiritual services and to have visits from their familiar pastor, rabbi, minister, or priest. When the spiritual provider comes to the home, both the client and caregiver may derive comfort from the visit. While most institutions provide chaplain services, the client may feel uncomfortable carrying out religious practices with an unfamiliar person or may not receive services as often as desired.

Comparisons of the costs of home care to institutionalization must be considered. The nurse should assist the family in determining which health care benefits apply to either the institution or the home. Short-term home care services are usually less costly than institutionalization. Medicare and other third-party payers often provide some coverage. Still, a short stay for intensive therapy in a hospital

may be less costly than the same therapy provided at home. Of course, the longer one is in an institution, the more rapidly financial assets deplete. To many elders, leaving a legacy to their family is an important part of self-actualization. Losing all of their assets to health care can be devastating to morale. Referring the client and family for financial counseling may be of great benefit for identifying various alternatives and providing the most cost-effective, quality health care services while maintaining a personal sense of worth.

### **The Caregivers**

If a client with health problems receives care at home from a family member, it is important to consider the caregiver's quality of life. Often it is the elderly spouse or an adult child who provides 24-hour care to the client at home.<sup>1,2</sup> A holistic approach to assessment of that person's health is appropriate as well. Physiologic health factors include a health history and a physical examination. Does the provider have health problems that could be affected by the additional work of caring for a family member? If the person is on a certain medical regimen, is he or she following it routinely? Does the schedule of care for the family member interfere with the caregiver's time to the extent that medications and treatments are forgotten and appointments for health checks are postponed? Is there time for adequate meal preparation? Is the diet for the client and the caregiver adequate? Does the caregiver have time to shop for groceries and other basics?

The physical environment of the home must be considered. Additions of hospital beds, assisting devices, wheelchairs, and the relocation of the client may be disruptive to the routines of the household and create potential safety hazards. The nurse should assist the family caregiver and the client in determining the best arrangements for convenience of care, comfort, and safety. Both the client and the family member draw a sense of security and cheerfulness if surrounded by familiar furnishings and family memorabilia.

## Quality of Life Issues in Home Care

Psychologically, the caregiver often experiences mixed feelings of love for having the opportunity to care for the family member, sadness for the loss of independence for both the client and the family, and uncertainty in preparing for the future. Caregivers experience frustration with the situation and may feel anger, anger that may be directed toward the client. Physical or mental abuse may occur. Nurses in home care must be aware of these possibilities and put in place preventive actions to avoid possible explosive situations. If the situation indicates a need, nurses should refer families for counseling services. Respite care for the provider is extremely important. Other family members, neighbors, friends, or health agency workers can provide the caregiver with several hours or days of time away from the home or time to tend to other household needs. A short holiday or vacation may be indicated. Examples of alternative care include a brief admission of the client to a health care facility or having someone stay in the home during the provider's vacation. Many volunteer groups provide friendly visitors, meal deliveries, and respite care for home care providers.

There seems to be a pattern of family relationships when a member requires intense care at home. Initially, when the family and the client first learn of a diagnosis that necessitates home care, family members are eager to assume total care. In later stages, when the client's health deteriorates and there is little or no support from professional health care providers or other family members or friends, the primary care provider's own health may become compromised. The caregiver becomes physically and mentally exhausted. Clients at home frequently become incontinent, are awake through the night, and become disoriented and demanding of the provider's care. Respite care or even the use of nurses' aides throughout the day and night may not provide adequate rest for the caregiver. The situation may worsen to the point that no other choice remains but to admit the client to an institution. The nurse should provide information to the client and family before the situation worsens and help them to

plan for future levels of care. Early intervention will prevent frustration, health problems, and even dangerous situations. The plan should include consideration of the client's and caregiver's feelings of guilt, failure, anger, or abandonment. It is important that everyone understands why the setting of care must change and how it can become a transition that is smooth and caring. Planning for the possibility helps members of the family and the client to feel a part of the decision and in control of the situation. Sociologic factors affecting the caregiver are much the same as those of the client. Health care beliefs and practices are important. Many cultures value care of the older generation and believe that the person must remain at home. Others prefer to have the client out of the home. Religious counselors can help the family by visiting the home to provide spiritual comfort and offer help from the organization.

The cost of home care can affect the financial security of the care provider. That person may give up employment to stay at home to care for the client. This loss of income will have economic and psychologic effects, yet paying aides or housekeepers may also drain financial resources. Frequently, these expenses are not part of health care benefits and must be paid for out of pocket.<sup>3</sup> Financial worries may greatly reduce the quality of life for the provider and elder. Again, referral to a financial advisor may assist the family in determining the best, most cost-effective approaches for caring for the client at home.

### Summary

Quality-of-life issues in home care are complex. Nurses not only must help the family consider these factors for the patient at home, but also they must examine the effects of home care on the primary caregiver and the entire family. Nurses use a holistic view in assessment to diagnose the needs of the client and the caregiver. Physiologic, psychologic, cultural, spiritual, and sociologic aspects are all considered. Nurses have an important role in

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assisting clients and their families to maximize the benefits of home care. They can help them with the provision of care in the current situation and to plan for the future for appropriate levels of care as the client's condition changes. These actions will result in an optimum quality of life for the client and the client's family.

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## Elder Care Recipients' Care-Seeking Process

*Cynthia K. Russell*

*The care-seeking process used by elders residing in a continuing care retirement community to elicit care from caregivers and engage caregivers in care interactions is described. Generated from 8 months of ethnographic field research that incorporated semistructured interviewing, participant observation, and focus group interviewing, data collection strategies with 47 elders, the care-seeking process emerged as the sequential phases and stages that evolved over time elders' interactions with their formal and informal caregivers. The findings extend what is currently known about the active and thoughtful role elders assume in their care interactions. An understanding of the ways elders elicit care and engage caregivers may assist nurses to maximize their care interactions with elders.*

Nurse researchers have identified care recipients' expectations of professional caregivers and care. Care recipients repeatedly expect caregivers to demonstrate professional knowledge and skill provide personalized care, maintain surveillance of care recipients, increase care recipients' participation in their care, be prompt, and have good interpersonal skills and personal qualities (Ashworth, Longimate, & Morrison, 1992; Brown, 1986; Cronin & Harrison, 1988; Grau, 1984; Larson, 1984; Rempusheski, 1988; Stockwell, 1972; Tagliacozzo, 1965; Tyron & Leonard, 1965). The foundation laid by these prior studies is helpful for evaluating what care recipients will likely consider as caring or noncaring interactions within their professional care relationships.

Over the past two decades, authors have documented a lack of attention to elder care recipients' perspectives of their care relationships (Barer & Johnson, 1990; Cotrell & Schulz, 1993; Dunkle, 1983; Lee, 1976; Parsons, Cox, & Kimboko, 1989; Thomas, 1987). Researchers are beginning to address this relative lack of knowledge and are laying a foundation for better understanding the lives of older adults who receive care from others.

*Cynthia K. Russell*, Ph.D., R.N., C.S., Assistant Professor, Department of Primary Care, College of Nursing, University of Tennessee, Memphis.  
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Recent literature represents an attempt to

understand more fully the lives of elders residing in nursing homes. Researchers have examined residents' perceptions of their care abilities (Atwood, Holm, & James, 1994; Sirovec & Kasno, 1993) and quality-of-care/quality-of-life issues (Clark & Bowling, 1990; Oleson, Heading, Shadick, & Bistodeau, 1994; Pearson, Hocking, Matt, & Riggs, 1993; Turner, 1993). Some researchers have documented the complexity of everyday life within the walls of nursing homes, thereby contributing to a better understanding of the care interactions and living strategies of elders in this type of facility (Daley, 1993; Gubrium, 1975; Kaakinen, 1992; Nystrom & Segesten, 1994; O'Brien, 1989; Tisdale, 1987).

An additional body of literature aids in our understanding of the care needs and care experiences of older adults in the home or the community. Current reported research has focused on three areas: elders' perceptions of health care needs and service use (Jackson, 1990; Laffrey, Renwanz-Boyle, Slagle, Guthmiller, & Carter, 1990; Roberto, Richter, Battenberg, & MacCormac, 1992; Schirm, 1989), life and living experiences of older community residing adults (Bates, 1994; Burke & Flaherty, 1993; Carlsson, Berg, & Wenestam, 1991; Miller, 1991; Schank & Laugh, 1990), and relationship issues between elders and caregivers (Russell 1994a; Trojan & Yonge, 1993; Wagnild & Grupp, 1991). Recent literature documenting the perspectives of older

adults in acute care institutions or hospitals is sparse and focuses primarily on quality-of-life quality-of care issues (Hall-Lord, Larsson, & Bastram, 1994; Laitinen, 1994) and interactions of elders and their caregivers (Armstrong-Esther, Browne, & McAfee, 1994; English & Morse, 1988).

A final set of literature is focused on the general experiences of elders as care recipients. Lustbader (1991) and Russell (1994b) have described the typical life experiences of older adults who are dependent on others for some type of care. Another set of literature that provides an insightful view of the everyday experiences of persons who receive care from others are autobiographies of care recipients (Friel-McGowin, 1993; Horner, 1982; Laird, 1979; Sacks, 1987). These works beautifully capture the complexity of living a life wherein one is dependent on others for some type of help or assistance.

A more complete foundation of knowledge about elder care recipients is being built; however, in the middle of this construction there has been limited attention to the strategies that elders use to seek and receive care from others. This interim period-- between the point an elder starts considering whether another's help is required and the point the elder evaluates the help received--encompasses the majority of many elders' everyday lives. Without a good understanding of some of the specific strategies elders use during this period, it is difficult for nurses or other caregivers to know how to offer and provide care or to understand what cues or signals older adults might use to elicit care from others. The research reported here builds on the foundation laid by prior research about elder care recipients as it focuses on this interim period, through a thorough examination of elders' care seeking.

### METHOD

Because there was limited knowledge about elders' perspectives on care seeking, the researcher used a qualitative inquiry approach of ethnographic field research (Pelto & Pelto, 1978; Schatzman & Strauss, 1973; Weaner &

Schoepfle, 1987), informed by the theoretical perspectives of symbolic interactionism and life span development. These theoretical perspectives acknowledge individuals as influencers of their interactions and development. Development is viewed as a lifelong potential, occurring via a dialectic process within the self, with others, and with society as a whole (Cook & Pike, 1988; Lerner, 1986; Stryker & Starham, 1985; Sugarman, 1990).

The researcher conducted 8 months of field research in the continuing-care retirement community (CCRC) of Paradise West (a pseudonym). Located on 32 acres in a planned retirement community in the southwestern United States, Paradise West had 249 apartments, 100 garden homes, and a 100-bed Medicare-certified intermediate and skilled health care center. Similar to other CCRCs (Fox & Abraham, 1991; Somers, 1993), Paradise West offered its residents a continuum of housing, including independent, congregate, and nursing home residence; residential services such as meals, social programs, housekeeping, and maintenance; support services such as personal care, respite care, or assisted living; and health care services, including intermediate or skilled nursing care and health care and illness prevention.

Forty-seven Americans of European descent participated in the study. Data were collected from semistructured in-depth interviews with 12 elders (27 hours total), participant observation in the facility's adult day care where 34 elders were observed (61 hours total), and a focus group with 4 elders (2 hours total). None of the focus group members had been interviewed or observed prior to the focus group, but 3 elders interviewed were also among the participants observed at the adult day care.

Complete demographics were obtained for elders who were interviewed or who participated in the focus group. Participants ranged in age from 76 to 88 years old (mean = 81 years). Approximately one fourth of the participants were men (3 in the interviews, 6 in the participant observation, 1 in the focus

group). Almost one half of the elders interviewed ( $n = 5$ ) and 1 focus group participant were married. Four of these 6 married participants were men. Most of the elders observed at the adult day care were widowed and living by themselves. On the average, participants had resided at Paradise West for 8 years.

Each data collection strategy had a different purpose and yielded different perspectives about elders' care seeking. The purpose of the interviews was to access individual elder's perspectives, eliciting detail and information about care seeking in an elder's own words. Participant observation, where the researcher assumed an observer-as-participant role (Gold, 1958), provided an opportunity to observe care relationships and care interactions between elders and their caregivers, allowing the researcher to enter the life world of the elders and view care seeking in terms of their everyday experiences. Although the individual interviews elicited perspectives of action, participant observation elicited perspectives *in* action (Snow & Anderson, 1987) the difference between what elders said about care seeking and how elders went about seeking care.

The purpose of the focus group fit with one of those outlined by Morgan and Krueger (1993), which was to identify the degree of consensus about the model of the care-seeking process. Therefore, the focus group was purposefully situated at the end of the research. At this stage, the researcher's interest was in obtaining a breadth of care-seeking experiences, to validate that the care-seeking process accurately represented the reality of these participants' experiences. The shared opinions and experiences of focus group participants supported the model of the care-seeking process presented in this article.

The researcher audiotaped most interviews and the focus group session in their end, immediately transcribing the tapes after each interview. Extensive notes were taken during the five nonaudiotaped interviews and typed into the computer at once after the interview. Note taking was distracting to elders and staff during

participant observation; therefore, the researcher made notes in nonconspicuous places. After leaving the setting, the researcher typed detailed descriptions of people, places, and interactions.

Data analysis proceeded concurrently with data collection, following the recommendations of Fetterman (1989) and Jorgensen (1989). Various types of data (cases, direct answers to specific questions, observations of specific incidents) were first compared, contrasted, and coded into as many discrete units as applicable, generating a code book of more than 150 codes with definitions. In the next step, the multiple codes were organized and reorganized into larger units and components to identify patterns, features, sequences, and relationships in elders' care seeking. As new insights arose later in data collection, leading to new codes, prior data were reexamined for the presence or absence of that information. Field notes and memos, written after each excursion into the setting or the data, were used to flag important issues related to the research process and key ideas about data analysis, such as the researcher's methodological reflections or theoretical ideas.

Care recipients shared their detailed experiences of seeking care and more than 275 cases were demarcated in the textual database. Case was operationalized as the description of a specific care encounter. Each case had specific structural elements, including actors, behaviors, and contexts. These cases were used to test the emerging care-seeking process. This step was useful for highlighting variations and exceptions to the care-seeking process, helping to circumscribe and clarify the sequence and meaning of the process.

An explicit purpose of this research was to investigate elders' care relationships with any persons they identified as caregivers. What emerged from the initial interviews and participant observation experiences, and was confirmed with each succeeding excursion into the field, was the lack of distinction between lay and professional caregivers in the minds and daily lives of these elders. The security guard or dining room staff were just as likely to be named as caregivers as the nurses in the care

center or the local hospital. The facility's social service director, who provided no physical care but did extensive care management, was more frequently mentioned in interviews than elders' primary physicians. A key finding of this research was that elders did not segment their caregivers into the commonly accepted formal and informal categories. We do not know if this finding was related to the ubiquitous nature of lay caregivers that increased elders' contacts with them, or if the elders actually made no distinction between the types of caregivers that are described in the gerontological literature. As presented, the findings reflect this lack of distinction.

## RESULTS

From the analysis of data, it appears that the care-seeking process comprises two phases: care eliciting and care engaging (see Figure 1). Initiating and alerting constituted the first phase of the care-seeking process. During this care-eliciting phase, elders planned and initiated calls for care and alerted others to their calls. Negotiating and evaluating constituted the second phase of the care-seeking process. In this care-engaging phase, elders participated in a give-and-take with their caregivers and appraised the need for continuing care. In Phase 2, care was actually accomplished; therefore, this phase was characterized by interpersonal encounters of varying types. The stages within Phases 1 and 2 are described in the following section.

### Phase 1: Care Eliciting

#### **Stage 1: Initiating**

The first stage of the care-seeking process began when elders decided the assistance of other persons was required or might be required. In this planning stage, elders' cognitive processes focused on the beginning steps for eliciting care for specific care occasions. This stage was termed "initiating." Two significant

components of the initiating stage were elders' preferences and elders' beliefs.

*Preferences.* Elders' preferences were the risks and expectations they considered as they made decisions to initiate care. A chief concern of elders was their desire to remain independent and this desire affected whether they would even initiate calls for care. Elders reported they actively chose to remain self-reliant, as exemplified in one woman's description: "I'm independent as hell too." After she laughed, the researcher inquired if that in any way affected what she asked other people to do and she said, "I suppose so, to a certain extent. Unlike a lot of people I plan ahead for things." A desire for self-reliance was evident among elders who were relatively healthy and active, as well as elders with serious health problems.

A more diverse preference was elders' expectations for who should initiate care. Elders reported and exhibited a range of care-initiation patterns, as displayed in Figure 2. At one end of the range were most elders, who related that they wanted to be the initiators of their care relationships, saying, "I'd rather call and ask someone for help myself." Though most elders prefer to be the initiators for their care relationships, others often stepped in to initiate care for them. Moving across the continuum of care initiation led to less active involvement on the elder's part for the origination of care. Representing the remainder of the range were elders who wished others could see what the elders needed and ask if they could help, or ask another person to help, or "just go ahead and do it." One woman who had a paid helper articulated her preferences for care origination in the following quote.

It's hard for me to ask her sometimes to do things. I think they [people she hires to help her] should see what needs to be done and go ahead and do it without being asked. I don't ask her to do more. I'm afraid I'll lose her. My daughter is concerned that my apartment isn't as clean as it should be. Anne [the paid helper] says she'd do whatever I ask....

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I'm afraid I'll lose her.

This elder highlighted the tensions that she felt in wanting her helper to do things that needed to be done without being asked, and knowing that things would not get done without asking the helper directly, but thinking that she might lose the helper if she asked her to do too much. Situations such as this were difficult for this elder, and others like her, who wanted to have things done differently but were reluctant to say anything to their caregivers because they might be left with no help at all. Little help was preferable to no help at all, perhaps because of the interactions that continued.

*Beliefs.* The second significant aspect of Stage 1 was elders' beliefs, which were their tacit understandings that affected who was defined as an appropriate caregiver and what unexpected occurrences they identified could result during their care. Beliefs were accumulated over time from multiple care interactions. Specific patterns of care initiating were dependent on the beliefs elders held. One belief centered on appropriate caregivers. Most elders described their decisions for selecting caregivers in this way: "you ask people to do things if it's their job to do them," and "you don't ask friends or family to do things if you can pay for someone else to do it or if it's offered by the facility." One woman explained her decision-making process in the following manner when the researcher inquired as to who she would ask if she needed something from the grocery store.

If I had someone, a residential aide that was doing that on a weekly basis, why I'd probably let them do it. Because I feel like my son has taken over the business end of what I have, why he's doing all that's necessary, since they give this

assistance here, why I think that I should make use of it rather than to call on my

family. Because that's the reason I moved here.

Similar decisions about selecting appropriate caregivers were highlighted during the participant observation component. Although most elders at the adult day care had a mild to moderate level of cognitive impairment, they typically requested care from appropriate persons who could respond to their calls for assistance. For example, elders generally asked the medication nurse or the center's director, both of whom were licensed practical nurses, for medications. The center's care assistants were more often asked to provide help with ambulation or toileting. Elders demonstrated a remarkable ability to distinguish appropriate caregivers from bystanders or caregivers that would be less likely to give the type of assistance they required.

A second belief was potential contingencies, which were the unexpected occurrences of care relationships that elders identified and, when possible, for which they planned. Elders believed they should plan for the unexpected, so that their care would be uninterrupted. Most elders believed they would experience an emergent care need at some time. In preparation for the unexpected, these elders modified their environments. Having someone check on them daily and having alert devices strategically placed throughout their living quarters, in case of a fall, were two key modifications. Beliefs of elders that they should avoid having their care needs conflict with their caregivers caused many elders to plan their calls for care around their caregivers' schedules or other jobs. One woman illustrated the efforts of several other elders in describing how she considered her caregiver's life beyond their care relationship by saying, "I try to work around her social life [when I think about asking her to do something]. She bikes,

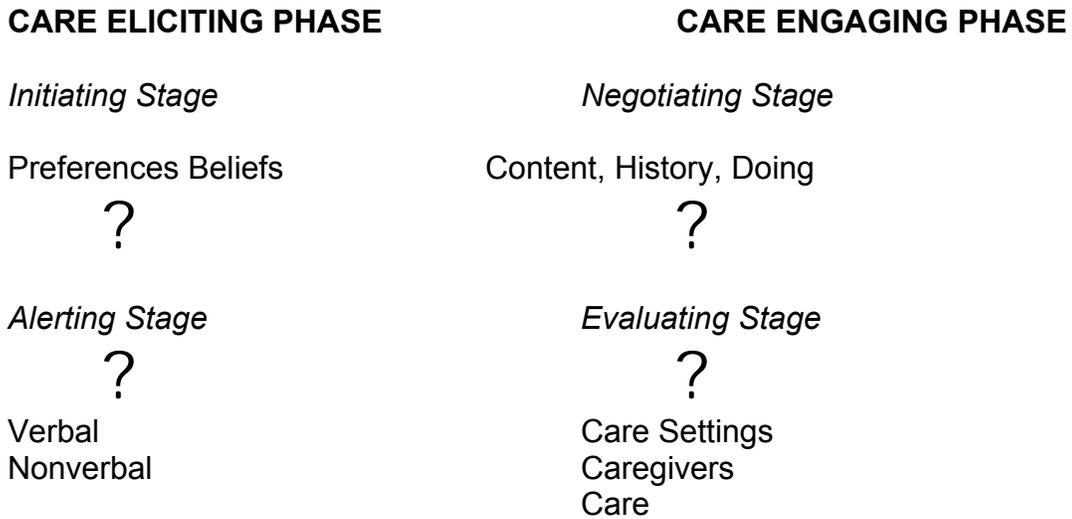


Figure 1: Sequence of the care-seeking process.

plays bridge, tennis and golf."

The length of time spent in the initiating stage was highly variable and often dependent on the specific circumstances of the care occasion. Progression emerged as an aspect of the initiating stage. For example, in emergencies, such as a fall or a stroke, the time and need for volitional initiatory planning was removed. In these cases, elders were unceremoniously and abruptly moved to the second stage of the care-seeking process. A participant observation example demonstrates rapid progression.

Marsha came out of the bathroom and she suddenly fell. Sandy [one of the nurses' aides] saw her going down and moved rapidly to go to Marsha. Roberta [the nurse] also came out of her office at that point in time and went rapidly to Marsha's side and said "Just lay there Marsha. Just stay down. Wait until I get Julie and we'll get you up. Are you okay?"

Lacking such an emergent stimulus, the other principal stimulus prompting movement to the alerting stage was a

conscious decision on an elder's part to seek care from another person.

***Stage 2: Alerting***

After elders engaged in their planning and decided to evoke assistance from other persons, the alerting stage began. Alerting related to how elders signified to others they required help or assistance. Elders alerted others to their desires for care using verbal and nonverbal strategies. Often, elders used several strategies for alerting simultaneously.

*Verbal strategies.* Verbalized alerting strategies included statements ("I need to go to the bathroom."), complaints ("I don't feel good."), queries ("Do I have any more medicine to take?"), expressions of preferences ("I would like to go home now."), and directives ("Get that chair out of my way!"). Elders combined various intonations with each of these verbalizations. Directives were the loudest and sharpest, apparent to all people in the setting, and were not typically directed to a specific person.

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Elder	Caregiver	Another Asks	Caregiver
Asks	Asks	Caregiver	Does
Caregiver	Elder	For Elder	For Elder

Figure 2: Continuum of care-initiation patterns.

*Nonverbal strategies.* Movements and volitional noises were categories of nonverbal alerting strategies. Examples of movements that alerted others that some help or assistance was required were raising eyebrows, going to the closet to get a coat, squinting at the light, and looking around. The earlier example of Marsha's fall illustrates how a specific movement called forth a response from caregivers. Volitional noises included sighing, choking, coughing, and noises assisted by a device, such as an alert call button, a pull cord in an elder's apartment that rang into the nurses' station, or a bell. Transition in the care-seeking process from Phase 1 to Phase 2 required an elder to initiate a call for care and alert someone to this call. When another person responded to the elder's call, the care-engaging phase commenced.

### **Phase 2: Care Engaging**

#### ***Stage 3: Negotiating***

Stage 3 began when a caregiver became engaged in an elder's care. This stage of interaction between elders and their caregivers around issues related to accomplishing care was described as "negotiating." The most important negotiation with caregivers was the content, that is, information and activities, elders would allow to enter into their care.

*Content.* The content of an elder's care negotiation developed over time, with differing circumstances and especially different caregivers sparking new negotiations. Although the content of care negotiations was variable, it

generally had the following components. First, elders wanted their caregivers to have an understanding of the purpose of specific care encounters. Elders sometimes engaged caregivers for discrete types of care. An example of this was a woman who was enrolled in a program where someone came to her apartment to check on her in the morning and evening.

She gets me ready for bed. But sometimes I'm not ready to go to bed at 9. Very seldom am I. So she stays until about 10 and gets some things done. There's bound to be little things come up that you can't do by yourself.

The primary purpose of having someone come to her home was to receive assistance with getting ready for bed. Secondary, the person coming in was expected to do the "little things" that the elder was unable to do for herself. She communicated her expectations to her informal caregiver, thereby ensuring the care encounter would meet her needs.

An understanding of the responsibilities and activities of elders and caregivers during care encounters was a second part of care negotiations. Elders sometimes explicitly related these, most often when negotiating with paid caregivers about what elders expected of them in exchange for payment. Finally, a temporal sequencing was described by elders as they indicated the order of events within a specific care encounter. At the adult day care, Linda spoke about the residential aide who helped her, describing the negotiation between herself,

Paradise West, and the residential aide.

She [the residential aide] comes in every morning, except holidays and weekends. That was one of the conditions for me going back to my apartment... I had to agree to change my bed [that is, alter it so it would be closer to the floor], have the girl to help me, and start coming over here. They [Paradise West staff] thought I needed to get out of my apartment and not just stay in there all the time without getting out. The girl is supposed to help me with my shower. I'm perfectly capable of doing that on my own. So she makes my bed for me. And then she'll pick up little things for me if I need them. My daughter keeps me pretty well stocked, but sometimes I need some things... Looking back on it, I really didn't think I needed to come here at the time. And I really didn't want to too badly. But I wanted to get back to my apartment. So I came. Now, I think it was probably a very good thing to get me out of my apartment. But I don't really need it now. But I keep coming anyway.

Negotiable items, in the prior example, included altering the height of her bed, allowing the residential aide to come into her apartment to assist her, attending the adult day care, and choosing the types of care for the residential aide to do (i.e., not her shower, but making her bed and picking up groceries).

Two significant aspects of the care-seeking process affected elders' outcomes in the negotiating stage. First was the historical components of relationships between elders and their caregivers. History provided a backdrop of prior interactions and negotiations, both successful and not so successful, which informed interactants in their present care encounters. When elders and their caregivers had several prior care encounters between them, care seeking was facilitated because they had other encounters to draw on to inform their

understandings of behaviors and communications in the current care context. An example from the adult day care demonstrated the benefit of history between an elder and her caregiver.

The van driver who was there to take Lynette to her dentist's appointment had walked over to Lynette with Roberta. Lynette started to get up; this takes her a minute or so usually as Lynette moves her walker around and scoots her chair around a bit. After telling Lynette about her appointment Roberta moved back a couple of steps. The van driver moved forward, reached down, and put his hands under her upper arms to help her get up. Roberta said to him, "She doesn't like for you to help her." He continued to keep his hands there and questioned, "She doesn't?" Roberta said, "No. She likes to do it herself." Lynette looked up at the man and smiled and he removed his hands. It took Lynette about a minute to get up, but she did it on her own.

In the prior example, the caregiver was able to effectively intercede on the elder's behalf because of their prior shared experiences. Without a historical backdrop, participants charted new interactional territory. In those instances, opportunities for miscommunication were increased.

The second significant aspect affecting the negotiating stage was doing, which related to whether elders did for themselves, or worked with others to accomplish their care, or if others did for elders. A continuum of doing emerged from informants' descriptions and experiences. Most elders preferred to do for themselves when possible, with their caregivers supplementing elders' efforts when necessary. In the following example of doing for oneself, a man described his experiences of doing something on his own, even after he was approached by someone else offering assistance.

Someone tried to help me out of the

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table chair after lunch one day and he knew I had problems. He came to my chair and tried to help me and I just told him, "Thank you. But I can do it myself."

In this instance, the elder acknowledged his unsolicited caregiver's offer of assistance, but expressed his desire to do things for himself. Actual experiences of most elders, however, showed that caregivers generally provided care *to* elders. In those cases, elders were not incorporated as participants in their care as they desired. One man described an experience with his wife, where his wife came in and dressed him without attending to his preferences to dress himself, even though he was trying to tell her he would prefer to do things for himself.

Something else came up and she came in here and had the things all ready to go and bang, bang, bang. And I told her, "Let me do it! I can do this stuff."... But she had things all ready to go and bang, bang, bang, I was finished.

To begin evaluating aspects of their care, elders needed sufficient information from the negotiating stage about which to make judgments. Once elders accumulated enough information in terms of negotiating care and doing the care, they began evaluating their care settings, caregivers, and care, thereby initiating the transition from Stage 3 to Stage 4 of the care-seeking process.

### ***Stage 4: Evaluating***

Stage 4 of the care-seeking process was the periodic appraisal, or evaluation, elders engaged in to decide whether there was a need for further negotiations around issues of continuing, altering, or disbanding their care relationships. Three characteristics marked this stage: elders' perceptions about care settings, caregivers, and care.

*Care settings.* All elders interviewed had

positive comments about the facility where they resided:

This place is a godsend. It's just wonderful. It's better than being in heaven, being here. They take care of you right and when you need something.

Several elders were reluctant to provide any information on any care setting that was of a negative nature, but after receiving reassurances of anonymity many offered their feelings about care settings that were not as positive. For example, one elder referred to a local hospital and stated, "I hope I never have to go there again."

*Caregivers.* Comments about different caregivers ranged from thinking an individual harsh to being truly appreciative of the caregiver's demonstration of caring. Caregivers were judged as **harsh** when they treated elders impersonally, were late, and demonstrated poor interpersonal skills. One woman's story about her experience with an ophthalmologist who diagnosed her macular degeneration represents elders' perceptions of harsh caregivers.

I said, "What's the trouble?" He said, "Well you've got macular degeneration."... I said, "Well, what exactly does this mean to me?" And he said, "Well you're going blind and you won't be able to see. You'll never be stone blind, but you're going blind and you won't be able to drive a car, you won't be able to play bridge or read." He just went through the roof and just threw it right in my face. I thought that was a little crude. Now I think that doctor could have had a little training.., he could have said it a little slower or he could have said, "Well," just gently. You see, when he was saying it, it was just wheezz, right into your face. And I thought that was pretty bad, I really did.

But that was the biggest shock. I really knew it, you see, and it was really being brought right home to me.

Those caregivers perceived as having affectionate and warm personalities, or those who went "above and beyond anything they had to do," were evaluated more favorably by elders. One woman's story represented those of many other elders as she described a residential aide who she considered "really special."

She acted like it was a pleasure to do what she was doing. She'd stop and get a breakfast bun and bring it to me in the morning; said she had one for herself. This is completely out of what they're supposed to do.

In this instance, which was similar to other elders' experiences, the elder perceived the residential aide enjoyed doing her work and was attending to the elder as a unique person in her own right, not merely as a nameless entity that required a certain amount of care before the time clock was punched to finish the day's work for pay.

*Care.* Elders varied in their descriptions of how it made them feel to receive care from others. Some described themselves as being fortunate and pleased, as noted by one man who said, "I guess I'm just happy about it. I'm glad it's available." Yet the vast majority of elders viewed receiving care as an obligation they did not like and wished they did not have to have, as suggested by one man's feelings about needing care after having a stroke: "This stroke killed me. I get so distressed and so down. Once every other week I wish I were dead." Another elder echoed this man's sentiments when she described her frustration with receiving care as omnipresent, "from the time you open your eyes in the morning until you close them at night."

## DISCUSSION

The care-seeking process generally proceeded as described, which point to the consistency of the situational forces and constraints that govern individuals as they interact with each other (Ross & Nisbett, 1991). Elder experienced frequent regularities in their everyday lives. Although man-potential options existed for daily life, elders' lives consistently reflected fewer number of regular possibilities. Elders counted on, and displayed, this predictability as they planned their lives and sought care. They deliberately used problem-solving skills and transformed the standard problem-solving method into a useful technique to assist them in seeking care.

Not surprisingly, because the theoretical perspectives of symbolic interactionism and life span development undergirded the research, the findings support viewing elders' care seeking as an interactional and developmental process. Some primary principles of symbolic interactionism include the human capability for self-reflection and evaluation, the negotiation of social reality in the course of social interaction, and the importance of experiences and meaning in interpreting situations and constructing courses of action (Blumer, 1969; Fine, 1990; Mead, 1934; Stryker & Statham, 1985). Selected principles of life span development include individuals a producers and products of their development, human plasticity, development as multiply-determined, the need for conflict to generate energy for continue development, and change as multidimensional and probabilistic (Featherman 1983; Lerner, 1986; Reed, 1983; Sugarman, 1990). Both symbolic interactionism and life span development recognize that social change and individual change are reciprocally and dynamically related. Symbolic interactionism recognizes the self emerges in social interaction and life spa development holds this person-environment interaction, wherein development evolves through communication,

to be integral. Similarly, both symbol" and life span development recognize the dialectical relationship of one's self and the world, in that the world has meaning only through one's embodied experience of it, but one's embodied presence has meaning only as it is actively engaged with the world.

Because paradigms and worldviews influence theory and research I: providing a set of blinders, a set of questions, as well as a set of answers' those questions (Hanson, 1958; Moran, 1983; Weekes, 1985), this section makes explicit how the theoretical perspectives described above contribute to an understanding of elders' care seeking. Elders in this study engaged I their care seeking and sought care by using their past experiences to inform them in their current care interactions. They demonstrated a capacity for self-reflection and evaluation by using their history of interactions, developed over time with various caregivers, to increase their insight into their care interactions (Russell, 1994a). As care recipients, these elders were in open interactions with their environment (specifically their caregivers and care settings) as they initiated, maintained, and evaluated their care relationships. Officially, an elder became a care recipient when another individual stood in the role of caregiver. A specific caregiver did not have to be physically present for elders to make judgments about their projected courses of action, however, because elders were able to creatively take the role of the other (a projected caregiver) in planning their actions. Taking the role of the other was also important for elders as they engaged in their dependency work--actively applying their cognitive and physical powers to initiate, maintain, and evaluate the'= care relationships (Russell, 1994b). When the regularities elders expected within their care encounters gave way to novel situations, they displayed great plasticity by making creative adjustments and counteradjustments in them: specific care-seeking behaviors. Even though they were faced with repetitive win-lose situations (with elders as the losers much of the time), elders continued to persevere, using each conflict as a drawing board for patterning future

interactions.

Although no person is totally independent of all other people, persons are often relegated to total dependence when they are no longer able to care for themselves in one or more aspects of their lives. The elders in this study and the descriptions from the literature would suggest this practice is one that should be avoided. Identifying who elders view as their caregivers and how elders view their clusters of caregivers may help formal caregivers, such as nurses, to maximize elders' care encounters with the various people who offer them assistance. Nurses need to listen to elders, to the amount of information and care elders believe they need, and to elders' indications, whether spoken or unspoken, that "enough is enough." Purposeful attention to these issues may help caregivers avoid inducing excess dependency in those persons they are trying to assist.

The findings of this study support the findings of others who have previously taken on the onerous task of investigating the complexity of older adults' everyday lives. The older adults in this study invoked a wide range of careseeking behaviors and strategies to meet their care needs. Most elders in this study desired to remain as independent and self-reliant as possible and, in cases where assistance was needed, to be involved as active participants in their care. This finding is congruent with those of Daley (1993), Nystrom and Segestea (1994), O'Brien (1989), and Tisdale (1987), and also corresponds to the resounding call for what might be termed "purposeful dependence" and active engagement described in care recipients' autobiographies (Friel-McGowin, 1993; Homer, 1982; Laird, 1979; Sacks, 1987).

Seeking care is a de facto part of the everyday life world, of not only the elders in this study, but also other persons who are situated within care relationships and require ongoing care. This part of everyday life is difficult to explore and time consuming to research and represent, yet it is where a significant number of persons spend a majority of their waking hours. The findings of this study support that the complexity of everyday life, the intersection of

care recipient and nurse, may be best understood through incorporation of multiple fieldwork methods, such as those used in this study. Without eliciting care recipients' verbal perspectives of action and also viewing their lived perspectives in action, the researcher would have had less sensitivity to the complexity and meaning of the care-seeking process. Further investigations of care seeking that would be useful include an examination of how individuals learn the rules of care relationships and the roles of care recipients, similarities and differences in elders' care seeking across different care settings and in care seeking of other individuals (i.e., children in day care), the relationship of early life patterns or experiences to seeking care, and whether differences in care-seeking occur when persons believe they will regain independence as compared to realizing they will be in a care recipient role indefinitely or forever.

The description of elders' care seeking demonstrates their abilities to participate as active agents in their care. Although nurses have paid lip service to older adults' participation in their care, elders have often been relegated to the role of passive recipients of care provision by nurses (Ashworth et al., 1992; Stevens, 1979; Tyron & Leonard, 1965). Care is typically provided to persons who are perceived as unable to care for themselves; thus they are identified, either implicitly or explicitly, as dependent. Although a need to receive care confers a dependency status on the care recipient, if nursing is truly a profession that has interpersonal relationships at its heart (Peplau, 1992), nurses must avoid an authoritarian-paternalistic role and foster older adults' autonomy. Nurses have an ethical imperative to work *with*, not *on*, older adults to enhance, rather than evade, their autonomy and human agency. Working with elders within care relationships demands that nurses exhibit sensitivity to the uniqueness of each elder, be aware of the different patterns that indicate a need for help, acknowledge the diversity of older adults and their aging processes, and attempt to tailor care to fit the unique

personality, specific preferences, and everyday life worlds of each elder.

As a central focus of nursing, care is a process occurring between a care recipient and a caregiver focused on the care recipient. Awareness of the strategies elders use to seek care provides nurses with the information they require to support current care practices or make research-based changes in practice. Nurses have an obligation to support care recipients in their care interactions. Conscious attention to working with elders within care relationships will reinforce the interdependence of those who receive and give care--a view that is more reflective of the reality of such relationships.

#### NOTE

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## Alzheimer's Disease

# **Part 7**

## **Ethical Issues**

## Alzheimer's Disease

# Physician-Assisted Suicide in Alzheimer's Disease

*Stephen G. Post, PhD*

This paper takes up the question of physician-assisted suicide (PAS) in Alzheimer's disease (AD), reviewing arguments for and against in a broad interdisciplinary context. Preemptive PAS-AD involving competent patients raises the further question of AD-euthanasia. The author concludes, after thorough assessment of the literature, that caution in moving toward AD-PAS is necessary. However, where PAS is legalized, it may be difficult to justify precluding people with AD from access. *J Am Geriatr Soc* 45:647-651, 1997.

The United States has entered the debate over physician-assisted suicide (PAS). Holland has refrained from prosecuting for PAS and euthanasia for several years, and more recently a territory in Australia followed suit. Referenda on PAS have been rejected in California and Washington State, but passed in Oregon, where PAS has been under a federal court decision invalidating the vote. Two federal courts invalidated state statutes prohibiting PAS, decisions since reviewed by the US Supreme Court. Pathologist Jack Kevorkian has continued his PAS activities in the national limelight, assisting several patients with the diagnoses of Alzheimer's disease (AD) or multiple sclerosis, both neurodegenerative diseases.

Advocates of PAS support legalization principally to reduce patient suffering and to enhance the rights of patients to retain control over their destinies. The person with a progressive irreversible dementia such as AD falls within these concerns, it is, therefore, timely to reflect on this issue, engaging the voices of an affected grass-roots population as well as expert opinion, while proceeding slowly and deliberately in order to avoid a superficial or hasty response. For demographic and other

reasons, increasing numbers of people will suffer from AD.

Alzheimer's disease - physician-assisted suicide has considerable social and historical significance. Local focus groups of AD caregivers in Greater Cleveland indicate moral differences of opinion. As one caregiver stated, "It is really a matter of positive, not negative, pride in who and what I am."

The framework for this paper emerged from a Plenary Address entitled 'Issues in Assisted Suicide,' presented to the Maine Bioethics Conference (The Acadia Institute, Maine Medical Association, Maine Bioethics Network), Augusta, Maine, October 6, 1995, and from a presentation entitled "Dying with Dementia," presented at the Amici Medicinæ meeting, Case Western Reserve University School of Medicine, September 18, 1996. A revision was requested for information purposes by the National Ethics Advisory Panel of the Alzheimer's's Disease and Related Disorders Association, and presented in December 1996. Address correspondence to Stephen G. Post, PhD, Center for Biomedical Ethics, School of Medicine, Case Western Reserve University, Cleveland, Ohio 44106.

"The state has no business telling me that I can't avoid a future that peels away my soul. Don't get moralistic about this." Another said, "Why restrict this to PAS when it is precisely when I am too far gone to make decisions and do things for myself that I would want to be die.' Some indicated that AD-PAS is (1) unacceptable because no one can know ahead of

time what the subjective experience of dementia is like, (2) inevitably biased by hypercognitive cultural values, (3) likely to lead to requests for voluntary AD-euthanasia (defined as mercy killing) and eventually to nonvoluntary euthanasia, and (4) likely to demoralize the movement to enhance long-term AD care.<sup>1</sup> More attention should be given to the opinion of AD-patients and their families on PAS and on many other ethical issues.<sup>2</sup>

This discussion begins with consideration of the AD population in relation to potential legalization of PAS; it then turns to the context of a healthcare system deficient in long-term and hospice care, to the possibility of AD-PAS leading to AD-euthanasia (this has allegedly taken place in the Netherlands), and to the need for satisfactory alternatives to AD-PAS that preclude over treatment of end-stage and of severely demented patients.

#### LEGAL RIGHTS AND ACCESS EQUITY

Currently, all the bills that state legislatures have considered to legalize PAS have required that the patient be certified as terminally ill (defined as likely to die within months) and competent, thereby excluding most AD patients because they generally do not fulfill the statutory definition of terminal illness until they have long since become incompetent. Is this exclusion unjust from a purely legal perspective?

One argument is that to avoid discrimination against people with AD, emerging laws should allow them preemptive PAS, i.e., assisted suicide while the patient is still competent to make such a serious choice and to then implement it with assistance. This argument need not be based on a conviction that PAS is morally compelling in most cases, but on a somewhat grudging appeal to nondiscrimination in the light of legalization of PAS.

The availability of PAS would allow the person with AD to avoid decline into severe dementia preemptively. The case of Janet Atkins illustrates this. One of her physicians described her as a 54-year-old married woman who developed memory impairment about 2 years

before her death.<sup>3</sup> Cognitive deficits included problems in reading comprehension and word-finding, making it "impossible for her to continue her career as a teacher and her avocation as a pianist". No longer able to play her classical favorites, but still able to play tennis well, she sought the assistance of Dr. Kevorkian while still competent.

In the Netherlands, where PAS occurs, the health system provides ample hospice and long-term care; even so, about 10% of requests come from patients with chronic degenerative neurological disorders. Battin writes of progressive dementia: "This is the condition the Dutch call *entlustering*, the 'effacement' or complete eclipse of human personality, and for the Dutch, *entlustering* rather than pain is a primary reason for choices of [active] euthanasia." She points out that in the Netherlands, PAS is based on intolerable suffering as determined by the patient. Suffering includes fear of the loss of personal identity.<sup>6</sup> The Dutch system, in theory, allows PAS or voluntary euthanasia only while the patient remains competent, although some reports indicate that euthanasia is occurring after the patient becomes incompetent.

Alzheimer's disease, Parkinson's disease, multiple sclerosis (MS), AIDS, and many other diseases are profoundly devastating without being immediately "terminal." Perhaps some significant percent of persons afflicted with these diseases desire PAS or euthanasia, but the laws put forward in the US, unlike practices in the Netherlands, preclude their access to PAS. Is this limitation excessively narrow? Much discussed 1994 guidelines were proposed for regulating physician-assisted death, justifying PAS and including patients with other than terminal illnesses, e.g., patients with MS. While the authors do not mention AD specifically, they could have.<sup>7</sup>

In contrast to MS patients, who often remain aware of their circumstances until death, patients with AD reach a point in the progression of disease when they "forget that they forget" and no longer have insight into their situation. Some may argue that the inevitable

cessation of requests for PAS attributable to loss of cognitive capacity make PAS unnecessary for AD patients, for they eventually drift into the "pure present" and do not thereby experience physical pain. Such a benign image of AD underestimates the anxiety and behavioral difficulties associated with this decline, and suggests, disturbingly, that the intact self has no moral authority over the inevitable decline of the deeply forgetful self. For patients with a diagnosis of AD, the fear is less that of pain than of the loss of self, a condition of such indignity in the minds of some that life would not be worth living.

However critical of PAS one might be, where legislation or judicial precedent permit PAS, it is arguable that people with AD must have the same legal right of access as those who are, by a narrower definition, in the "terminal condition." AD is perceived by many people in our society as a death before death -- a partial to full death of the mind while the body lives on. This view is simplistic, but in advanced dementia the condition of having no self identity (no temporal connections between past, present and future) is often approximated. Even if some percentage of patients do adjust emotionally to their condition, not all do. Further, those who take pride in themselves as fully capacitated and intact selves will not rest content with state interference in a highly personal decision.

### **THE INCOMPATIBILITY CONCERN**

Yet, such an opening for pre-emptive AD-PAS could affect societal and familial resolve to provide optimal long-term and end-of-life care as an alternative. AD-PAS is cheaper than long-term AD caregiving. Sulmasy suggests that in a managed care system, assisted suicide and euthanasia would be attractive to managers for financial reasons? As managed care and PAS converge, the latter may alleviate pressure on managed care to develop long-term care and hospice for end-stage AD patients. The American Geriatrics Society's Ethics Committee raises this same sort of concern: "Legalization of physician-assisted suicide might thwart society's resolve to expand services and

resources aimed at caring for the terminally ill, dying patient.<sup>9</sup> This hospice concern is directly relevant to patients with end-stage AD and bears on long-term AD care generally, which is underfunded,<sup>10</sup>

The exclusion of people with AD from access to PAS could be based on a concern that both long-term care and hospice for end-stage AD patients are deeply inadequate in the US. Rejecting PAS for AD patients forces society to focus on developing these alternatives more fully. This is by no means a new line of argument among critics of PAS.<sup>11</sup> Why persist with expensive long-term care and AD-specific hospice when life can be ended cheaply consistent with autonomy? Better to devote resources to the development of therapies for AD.

However, the statement that prohibition is the only spur to progress should not be accepted uncritically. Perhaps the legalization of PAS for AD patients would accelerate the search for a cure or for better forms of care. By analogy, few things have mobilized the movement to improve care at the end of life better than the passage of the Oregon PAS law. Similarly, the passage of *Roe v. Wade* in 1973 seemed to spur the right-to-life movement, and the acceptance of the right to withdraw or withhold life-sustaining therapy did not preclude the development of new and more advanced life-saving therapies.

Still, legalization of AD-PAS may preempt development of adequate AD-hospice or long-term care where such care does not already exist. This hypothesis is dependent upon contextual factors, including political and cultural pressures, the interests of researchers, and the activism of patients, risk groups, and family members. Where PAS for people with AD is permitted, for example, it is likely that advocacy groups such as the Alzheimer's Association would still press for better long-term care and basic research leading to a possible cure or, more realistically, to prevention. Furthermore, the availability of PAS might spur its opponents to mobilize resources to develop state-of-the-art comfort and long-term care systems.

In reality, the person with a diagnosis of AD who desires PAS will probably not be much impressed by concerns about spurring progress. Why should the patient be concerned with some hypothetical future healthcare system ideal? Does this not reduce the patient to a means? Nevertheless, if PAS for people with AD is implemented in the absence of a reasonably adequate and accessible care system, the following may occur: (1) diversion of funds from AD long-term care and AD-hospice; (2) limitation of physicians, nurses, and other staff training for these facilities; (3) diminished research in these forms of care. Hospice personnel prefer to err on the side of caution. Miller's survey of hospice staff (including nurses, physicians, administrators, social workers, and volunteers) indicates that only 5% favor assisted suicide, and only 1.5% favor mercy killing, whereas 55 to 65 % of respondents in public opinion surveys favor these options, although many surveys present false dichotomies and are poorly worded. The major reason for this opposition among hospice staff was that it would "divert attention away from efforts to provide optimal palliation and more appropriate and compassionate terminal care."<sup>12</sup>

Even if we see more hospices in the future that include PAS, AD patients in such environments would be in the end stage and therefore incapacitated with respect to decision making. They could not assist in their suicide. Thus, AD-PAS raises the likelihood of voluntary AD-euthanasia based on prior request while still competent.

#### **FROM AD-PAS TO AD-EUTHANASIA?**

The statement quoted at the outset of this paper, "Why restrict this to PAS when it is precisely when I am too far gone to make decisions and do things for myself that I would want to die," has significance.

It is deemed widely appropriate to halt the momentum of invasive technologies in severe AD. AD-PAS lies between treatment limitation and euthanasia, but it is much closer to the latter. In PAS, the final act is carried out by the patient; in euthanasia it is carried out by

someone else. If AD-PAS is permitted when the patient is still competent, then why not permit life to be ended based on prior request after the disease has progressed to the end-stages, or perhaps to the severe stages when self-identity seems profoundly compromised? Arguably, the rejection of requested AD-euthanasia fails to serve the needs of patients.

On the other hand, to keep a patient with advanced dementia comfortable requires neither causing death by human hand nor striving for prolongation. Euthanasia (mercy killing) is not a desirable option because of the possibilities for abuse and, according to medical tradition, because it confuses the art of healing and comforting with the practice of killing. One reason that the Hippocratic Oath forbade physician-assisted killing was that physicians in antiquity were viewed more as executioners than healers and were consequently distrusted by the public.<sup>13</sup> Moreover, voluntary euthanasia can become nonvoluntary. For example, four Austrian nursing aids allegedly killed 49 older demented residents in a long-term care setting several years ago? Senicide (nonvoluntary euthanasia) can be an attractive option to the caregiver who is finally just burned out or to the society that cannot afford to pay for long-term care. Anthropologists are quick to point to cultures in which senicide was considered both just and, on the part of the very frail, virtuous.<sup>15</sup> During the past decade, at least several cases of care-givers killing severely demented spouses have been in the limelight, with one Florida man convicted of murder and jailed. The possibilities for abuse of AD-euthanasia are vast, including the emergence of nonvoluntary euthanasia.

#### **AVOIDING OVERTREATMENT: DOES THIS SUFFICE?**

An approach to dying with AD that would avoid PAS and euthanasia, as well as overtreatment, takes the patient's precedent requests (via a living will and/or a durable power of attorney, for healthcare) for nonaggressive care with full seriousness.<sup>16</sup> Although critics of this view contend that those who request limited life-extending care simply

do not appreciate the potential quality of life in being demented, such a view could hardly be more disrespectful of patient self-determination.<sup>17</sup> Indeed, this unfortunate unwillingness to take precedent autonomy seriously underlies some of the appeal of AD-PAS. After all, if healthcare institutions and professionals ignore the moral authority of patient autonomy as indicated through advance directives, then PAS becomes the only option. Indeed, if the "then" (intact) self knows it will have no say in the treatment of the self when severely demented, then voluntary AD-PAS should be allowed. The possibility of AD-PAS should spur policy makers to ensure that competent requests for treatment limitation are respected in the AD population. Perhaps the only real spur toward respect will finally be legalization of AD-PAS.

Such pressure, however, ought not to be necessary. One way to encourage respect for the precedent autonomy of people with a diagnosis of AD is to endorse strongly the presence of hospice levels of support in AD patient care, beginning with the terminal stage of the disease. There are now several thousand hospices and many more hospice services in the United States that serve cancer patients predominantly, and, in much lower numbers, AIDS and cardiac patients. While AD patients have been denied access to hospice in the past, a significant percentage of hospice patients are now in nursing homes, and the number of patients included with end-stage AD may, therefore, be growing rapidly. Hospice is not best defined as a locus of care since hospice care can be provided in hospitals, residences, and nursing homes as well as in hospice centers. In selecting hospice, a person decides on a philosophy of care emphasizing comfort and quality of life in contrast to life prolongation except as a side-effect of palliative treatments. This philosophy can be chosen and implemented in a wide variety of settings, usually with the help of a hospice team.

People with end-stage AD or other progressive dementias have not readily fit the hospice mold for several reasons. First, the person will ordinarily lack the decision-making

competence to select hospice, except precedently by advance directive, and will have less cognitive capacity in hospice than will most cancer patients. Second, many hospices only admit patients who are likely to die within 6 months, although this Medicare reimbursement policy may be revised. A new model clarifies the probability of dying within 6 months following the onset of a fever in people with advanced AD. Used in combination with clinical judgment, this can indicate patients for Medicare hospice coverage.<sup>18</sup> The person with end-stage AD is often thought to be free from pain, in contrast to the cancer patient. But there may be more pain and discomfort in these patients than might otherwise be supposed, and there are ways in which they can be made more comfortable by properly trained hospice personnel familiar with AD.

A hospice approach is increasingly considered highly appropriate for the care of people with advanced dementia? A significant majority of physicians (61%) affiliated with the American Geriatrics Society, as well as a sample of family caregivers (71%) associated with the Alzheimer's Association, favor hospice care in cases of end-stage dementia.<sup>20</sup> For many people with severe dementia who lack insight into their surroundings and the intentions of others, aggressive medical interventions can be interpreted as torturous, violating the principle of "do no harm."<sup>21</sup>

In a 1991 cross-national study of physicians' attitudes toward life-extending treatment interventions in cases of older people with severe dementia, considerable disagreement was evident? The authors prepared a questionnaire asking, "What decisions would physicians make when confronted with a critically ill, demented elderly man?" They presented the case of an 82 year to 91 year old man with life-threatening gastrointestinal bleeding who 3 years earlier had been diagnosed by a neurologist as suffering from probable AD. He cannot answer a simple question coherently, but seems to understand some simple commands. His behavior is agitated, he wanders, does not recognize his daughter, and has urinary incontinence. In seven countries, physicians in academic medical

centers at family practice, internal medicine, and geriatric rounds were questioned about their views on treatment levels. The authors concluded that there is wide variation of opinion both within and among countries. For example, only 6% of Australian physicians recommended treatment in a medical intensive care unit, whereas 32% of US physicians did so. Conversely, 21% of Australian physicians chose supportive care compared with only 3% of US physicians. The variation that this study found is difficult to interpret because no underlying explanations for it are discussed, e.g., financial, moral, religious, or cultural.

Several philosophers have recently argued that as dementia progresses in severity, only supportive care is morally fitting. Brock asks, "What health care and expenditure of resources on health care is owed on grounds of justice to the severely demented elderly?"<sup>23</sup> He concentrates on the effects of dementia such as the erosion of memory and other cognitive functions that "ultimately destroy personal identity." This loss implies, for Brock, that the "severely demented have lost an interest in treatment whose ultimate purpose is to prolong or sustain lives." They retain, however, an interest in comfort so that a painful tumor might be removed for palliative reasons.

Callahan points out that for the patient who is severely demented, "On the one hand, he has lost his capacity for reason and usually -- but not always -- human interaction. On the other hand, there will be no clear ground for believing that the capacity to experience emotions has been lost."<sup>24</sup> Callahan's conclusion is that "death need not be resisted."

As early as 1976, Robert Katzman wrote "In focusing attention on the mortality associated with Alzheimer's disease, our goal is not to find a way to prolong the life of severely demented persons... "<sup>24</sup> Unaware of environment-mute, bedridden, incontinent of bladder and bowel, with unmeasurable intellectual functions, and with death inevitable, comfort care is often all that medicine should offer. Comfort care means palliation only, i.e., it excludes artificial nutrition and hydration, dialysis, and all other

medical interventions unless necessary for the control of pain and discomfort. Some treatments, for example antibiotics, can be intended for palliation and comfort care but will extend life as an unintended side effect.

The problems in developing hospice care for end-stage AD are considerable but not insurmountable. Yet, such care does not provide a full alternative to AD-PAS and AD-euthanasia since it fails to address the right to limit life-extending care in the moderate stages of AD when the patient may have indicated precedently that he or she would not want to experience this decline in self. It is worth recalling the Struldbruggs described by Jonathan Swift in *Gulliver's Travels*. They suffered complete loss of memory coupled with immortality. Swift suggests this image as a reminder to observers that death "need not be excessively feared."<sup>26</sup> If new drugs become available that may slow the progression of AD, there would be many who would find the protraction of morbidity undesirable, at least beyond some threshold point of incapacitation.

## CONCLUDING RECOMMENDATIONS

It is important to emphasize the clinical and moral rationale for hospice care in the end-stage of AD, thereby ensuring families that the choice of this level of care is acceptable and reasonable. Hospice is a pathway that should be sanctioned widely by advocacy groups and healthcare professionals. It is also important that treatment limitations be routinized in the moderate stages of AD according to advance directive or family entrustment.

The movement toward PAS and euthanasia is one of social importance that will impact the AD-affected population profoundly. Although it cannot be responsibly accepted without much further deliberation, neither can it be ignored because anecdotal reports indicate some rational AD patient., in early stages of the disease do make this request while they still can. Further deliberation on the matter of PAS means, in effect, being critical of the decisions of the 2nd and 9th Circuit Courts of Appeals because these

decisions are judicial impositions that preempt the needed public debate in the AD-affected population. There is also reason to worry that these court decisions are occurring in a period when societal commitment to the frail and undesirable seems to be shrinking.

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## Alzheimer's Disease

# **Part 8**

## **Transitions**

## Alzheimer's Disease

# **Alzheimer's Disease Caregivers:**

**The transition from home care to formal care**

**by Marie Theresa Duncan, Ph.D.**

Portland State University, 1992  
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## Alzheimer's Disease

## FORWARD

A move of an Alzheimer patient to a nursing home or other formal care facility does not mean the end of family caregiving. Instead, the family's caregiving activities must be integrated with the ongoing efforts of the formal care staff. Currently, relatively little is known about 1) what families experience in making that shift and 2) the relationship between family caregivers and paid staff in formal care settings. 3) Recognizing this as a time of transition for these family care-givers.

Three research questions were identified:

- 1) What do family caregivers to AD individuals experience as they shift their caregiving from home to formal care settings?
- 2) How does caregiving in formal care differ from caregiving at home?, and
- 3) How do family caregivers perceive the relationships that develop between families and formal care staff? Specific attention was also paid to the experiences of both spouses and adult children.

A qualitative approach provides an especially useful methodology. Grounding the study in the world and experiences of caregivers is not only appropriate for increasing knowledge but also practical for exploring new areas.

Two specific bodies of data were investigated. First, transcripts of a series of 30 focus groups with 179 caregivers who were providing care either at home or in formal care settings were analyzed. Second, ten follow-up interviews were done with 12 caregivers who had previously been involved in the focus groups while they were providing care at home and who had since placed their family member in formal care.

There comes a time to make the decision that results in the transition to formal care. Both spouses and adult children overwhelmingly identified physical exhaustion and often emotional exhaustion as the pervasive common theme. After reaching this state, the caregivers identified turning points that had contributed to the placement decision. While the literature has often pointed to the importance of crises in caregiving decisions, the findings of this study, while not negating this, also call attention to the pivotal nature of events. These kinds of events turn out to be more like turning points than crises.

Caregivers in this study identified five themes that were influential in their decision-making process. In order of their importance to the caregivers, they were: events, the health care system, caregiver-care receiver relationship, support, and options and availability. By themselves, these factors did not necessarily predict placement but, in combination, there was a profound effect leading to placement. Themes of family and surviving remained consistent throughout all phases of the transition to formal care.

A male spouse caregiver was more likely to make a decision for placement following a turning point event that centered on an incontinence problem, while a female spouse caregiver was more often moved to action by an AD safety issue. The health care system was usually a negative influence and served to delay the placement decision. Within the caregiver-care receiver relationship, the influence of past experiences and perceptions was extremely powerful, but support did not receive the degree of influence that the caregiving literature has suggested. Finally, even if a family had its care receiver's name on a waiting list, it was rare that an opening was available at the time of need.

A real paradox happens at the time of the placement process. Caregivers are 'trying to hold on while letting go. Immediately, family caregivers noted shifts in three major areas: control, involvement and personal reorganization. They noted an intense 'roller coaster' effect. Most often their first mention was of guilt. Caregivers found the new experience of confronting a unit of AD residents an

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overwhelming beginning experience. In reflecting on the evolving process of participating in formal care, caregivers frequently noted the development of a caregiving relationship with staff. The individuals whom the family caregivers mentioned most often were the aides. Even though a complex organizational environment exists in a nursing home, family caregivers expect sensitive and professional behavior toward not only the resident but also toward themselves. Their bottom line was that staff delivered quality care, which they equated with caring about the resident rather than merely taking care of them.

The findings from this study have implications for theory development, family caregivers, formal care staff, and health care policy.

# INTRODUCTION

It is widely known and accepted that families take care of an older family member during illness. The hope for most families is to be able to provide the necessary care at home. Recently, there has been considerable research directed toward helping families accomplish this task. However, there are times this is not a manageable goal. Cognitive impairment in the care receiver is often a significant contributor to the move to formal care. The overwhelming difficulty of providing 24-hour care contributes to more than three-fourths of Alzheimer's Disease (AD) caregivers placement (Stephens, Kinney, and Ogrocki, 1991).

This study investigates the experience of family caregivers to Alzheimer's Disease care receivers as they make the decision which ends their ability to provide caregiving at home and shifts the setting to formal care.

The cause of Alzheimer's is unknown, but the devastation of the progressive and irreversible brain damage leaves the individual completely dependent and very vulnerable to Institutionalization. Also, AD is the fourth leading cause of death among older adults (Blieszner and Shifflett, 1990). The significance of this situation is noted in the fact that AD and other forms of cognitive impairment are the major causes of nursing home placement and at least 50 percent of residents in nursing homes suffer from some type of dementing illness (National Institute of Health, 1981). Because of the often gradual change in the individual's behavior and ability to function, family members find themselves involved in a caregiver's role. After a period of time that varies widely, family members find it necessary to seek professional help and resources. This shift from caregiving at home to a formal care setting results in major changes for the older individual, the family caregivers and the extended family.

The family's response to providing care to our aging population has been well documented (Bengtson, 1989; Brody, 1985; Lerner, Somers, Reid, Chtriboga and Tierney, 1991; Shanas, 1979b, 1980; Treas, 1977). In the past decade there has been considerable research on family caregiving at home (Barusch, 1988; Cantor, 1980; Gwyther and George, 1986; Horowitz, 1985a; Miller, 1986; Zarit, Reeve and Bach-Peterson, 1980). It has been recognized that family caregiving continues after the move to formal care (George and Gwyther, 1986; Stephens, et al. 1991). Although research on families and formal care can be found, very little organized attention has been given to experiences of family members of institutionalized dementia patients (Bowers, 1988; Pratt, Schmall and Wright 1987a; Pratt, Schmall, Wright and Hare, 1987b). The need for research on the family has been identified as an important area in Alzheimer's Disease (Ory, Williams, Emr, Lebowitz, Rabins, Salloway, Sluss-Radbaugh, Wolff and Zarit, 1985).

In the past, institutions, specifically nursing homes, have been viewed by the public as places that smell bad, are warehouses, and where care is often inadequate if not abusive. Families who institutionalized their family members often felt society judged them guilty of abandonment. In AD however, while the physical and mental status of the care receivers and often the caregiver deteriorate, the family ties do not (Bengtson, 1978). The working team prior to institutionalization has been the caregiver and the care receiver. The caregiver has had to negotiate this course in often unclear circumstances involving a disease process, medications, new services and the health care delivery system. Once the shift to formal care is made, the caregiver-care receiver dyad changes to a triad with the addition of formal care staff. Now the course is still undefined and vague, but caregivers must chart it within the confines of a formal institutional setting. They may be required to do more than they want or may feel cut out of care they desire to give.

In general, early research shows that technical tasks involving physical care are provided by staff and nontechnical tasks involving emotional or psychosocial care are more likely to be provided by

family (Fauerbach, 1984; Litwak, 1981). Yet, other studies direct attention to the ambiguity that surrounds specific responsibilities of staff and families in relation to patient care (Rubin and Shuttlesworth, 1983; Shuttlesworth, Rubin and Duffy, 1982). Bowers (1988), found that caregivers were more likely to perceive their caregiving by its purpose rather than with a task focus. While research provides increasing knowledge about family caregiving in formal care, a key point remains, the quality of nursing home care appears to benefit when families remain involved with their institutionalized relative (Shuttlesworth et al. 1982). As discussed above, with the gradual deterioration of the elder, families find themselves in a caregiver role. In exploring family caregiving it is important to recognize that the individuals who provide direct care most often are the spouse or adult child. Caregivers have been predominantly wives and daughters (Johnson and Catalano, 1983; Brody, 1981), although some husbands do care for their demented wives. As parents age and spouse caretaking takes its toll, adult children are called upon to assume increased multigenerational caregiving demands.

Children who find themselves in a caregiver role feel more strain than do spouse caregivers (Johnson and Catalano, 1983). Spouses report poorer physical health and well-being along with more stress symptoms than adult children (George and Gwyther, 1986). If we compare spouse caregivers of dementia patients, Fitting, Rabins, Lucas and Eastham (1986) found women were more distressed than men and the younger wives felt more lonely and more resentful of their role than the older wives.

Thus much remains to be discovered and understood about the move from family caregiving at home to formal care. It is also important to explore family caregiving to the institutionalized dementia patient and how it effects the different types of caregivers. Greene and Monahan (1987) point to the increasing interest in the nature of the caregiving relationship and the experience of its participants because of a recognition of its importance at a system level. Recognizing the patient-centered focus in formal care, Pratt et al. (1987b) has described the family caregivers to institutionalized dementia patient as "forgotten clients."

### **PURPOSE OF THE STUDY**

The purpose of this study is to contribute to the knowledge base about family caregivers' transition from home care to formal care. This study is limited to family caregivers of elderly with Alzheimer's Disease. It is an especially important study since research on family caregiving in formal care settings is in an early stage of development. Exploring the shift from home to formal care will allow for an investigation of the caregiving placement decisions, early formal care adjustments and development of the family-staff relationship. This will provide for a longer-term view of caregiving as on a continuum which can be explored as phases which evolve over time. In this view, Institutionalization is not a separate or end event, but reflects a continuation of prior caregiving experiences. This research will also explore the differences and similarities between spouses and adult children in what they do and how they feel about this caregiving transition.

### **TRANSITION CONCEPT**

This section identifies the basic theoretical concept. The concept of transition provides a direction for the conduct of this study.

#### **Transition**

Transition invariably is related to change. It can be viewed as a period between fairly stable states; or 'linking change with experienced time' (Chick and Meleis, 1986, p. 239); as a bridge or a boundary zone between the two more stable states (Levinson, 1978); or an ending, neutral zone and new

beginning (Bridges, 1980); or a period of moving from one state of certainty to another with an interval of uncertainty and change in between' (Golan, 1981, p. 12). Parkes (1971) writes of psycho-social transition which conceptually is merged from stress, crisis and loss research. Individuals most often resist change. The reactions they experience are often influenced by their prior experiences and the way they perceive what is happening. These reactions span a spectrum from viewing change as a rite of passage, to being considered an individual weakness requiring attention (Silverman, 1982).

Transition contains the elements of process, time span and perception (Chick and Meleis, 1986). Process involves disruption and suggests phases, such as a shift from what was, into confusion, then to a new beginning. The individual's response to the disruption is part of the process element. Time span implies elements of both an ongoing activity yet suggests a bounded phenomenon. Finally, perception offers a clue to the meaning of the transition to the person to whom it is happening. It often is associated with role ambiguity and threatens the individual's self-concept. Golan (1981) classifies transitions by time periods, role shifts and marker events. Time periods refers to the life cycle and movement through chronological stages influenced by biological, psychological or social events. Role shifts implies a change or acquisition to a new social role with its inherent need for adaptation. The incident which triggers the beginning of the change and often shapes the time of change is known as the marker event. Thus, a transition may be viewed as a series of personal experiences and adaptations.

The work required in a transition is related to the suddenness of the onset of the condition, the amount or degree of loss to the individual and how much of his life is touched by the situation (Silverman, 1978, p. 12). Transitions can vary by several dimensions which are often presented with dichotomies, such as minor disruption vs. major disruption, temporary vs. permanent, desired vs. undesired, and planned-predicted vs. unplanned-unpredicted (Chick and Meleis, 1986).

Transitions are not experienced in a uniform way, even when the actual situation, such as caregiving, is similar. They do have commonalities of a beginning or entry into, the going through or passage and/or exit. As cited above, specifics about the dimensions would help generate information about the entry. An important part of the passage phase is the meaning the situation has for the individual. As the individual exits, outcome is often spoken of as the level of well being. In summary, transition involves a passage from one state, phase or condition to another. It is a personal process and it results from complex person-environment interactions.

For the purposes of this research, a transition model developed by Bridges (1980) will be applied. Bridges' (1980) perspective is particularly useful because most discussions of transition treat a change or stressful life event as the beginning of transition. Bridges (1980), however, provides a contrasting approach which presents transition as starting with endings, followed by a period of distress and confusion, called the neutral zone, and finishing with a new beginning. By examining the underlying patterns involved, an attempt can be made to better understand the process. He states, "... it is based on a theory of personal development that views transition as the natural process of disorientation and reorientation that marks the turning points of the path of growth". Bridges (1980) starts the transition process with an ending. He notes that too often we take transition as an end point rather than identifying it as the very point where, upon recognition, one can actually begin anew. In the neutral zone there is confusion and disorganization, a disconnection with the past but not yet an emotional hook-up with the present. The new beginning calls for internal action, not just reaching the point by being a survivor.

### **Endings**

Letting go is a difficult task and one tends to let go of most of the external ties before making the necessary internal ones. As an ambiguous process, this is why one tends to come back to old ways. However, before one can move to the new, one must let go of the old. During this phase, individuals bring previously developed styles which they sometimes recognize and other times don't. Bridges

(1980) notes, 'One of the reasons that it is so difficult to assess things is that the impact of transition upon us does not necessarily bear any relation to the apparent importance of the event that triggered it off'. If individuals reflect on their style, it can be useful to explore what pieces are actually theirs and those that belong to the influence of others, culture, and social dictates. When a transition involves more than one individual, they obviously may come to points of separate and personal transitions. Bridges (1980) identified four aspects of the natural ending experience: disengagement, disidentification, disenchantment and disorientation.

Disengagement results in a break with the familiar and this helps change the old familiar clues which reinforce the role and past behaviors. Disidentification is the internal capturing of the loss of familiar roles and labels. In disenchantment, the individual discovers, or even begins the transition with some sense their world is now no longer real. This experience is often the initial clue to transition. Disorientation is a time of confusion and emptiness when common things from the past take on an unreal quality. The basic essence to endings is that often this aspect is so difficult one isn't sure of surviving the challenge to self.

### **Neutral Zone**

The common descriptors for this time are feelings of emptiness and loss. Bridges (1980) notes, 'The neutral zone is not an important part of the transition process -- It is only a temporary state of loss to be endured' (p. 112). Common behaviors are often captured by labels of inactivity and ritual. An inner reorganization occurs during this time and the individual must first surrender to the feelings of emptiness and loss. It is during this time that self-renewal occurs, a new perspective emerges, and opportunity for insight occurs.

### **New Beginning**

In Bridges' (1980) model, one comes to the beginning only at the end. Inner, subtle signals will alert the individual that changes are occurring which result in feelings of renewal. 'New beginnings are accessible to everyone and everyone has trouble with them'. A critical feature of this personal time is to do more than "just hang in there." While an external new beginning may appear early on, the individualized work involved in the inner beginning occurs more slowly. With this hard work, the individual should remember to take a time out, be patient with himself and engage any known supports that helps him through this job.

Bridges' (1980) model will be applied to the family caregiving situation in AD and evaluated as to its fit. One of the goals is to assess how apt a conceptual framework it will prove to be. It is recognized as an adequate organizing framework, but will it be able to help further the understanding of the transition to formal care? Do family caregivers experience ambiguity in their decision-making time, and once they have accomplished placement is there a period of disruption and confusion? Is it possible for these caregivers to experience anything closely resembling a new beginning? Thus, will this model help us better understand caregiving in general and placement into formal care in specific?

In summary, this transition model by Bridges (1980) starts with an ending, moves to a neutral zone and is completed with a new beginning. Since one experiences many changes in one's life, these transition excursions are like side trips off the main road only to return to the freeway of life.

A quote from Ralph Waldo Emerson (1965) is appropriate: "Not in his goals but in his transitions man is great."

As might be implied above, these family caregivers are at an exceptional level of commitment and intensity when they are involved in this particular transition work. The concept of transition provides a framework for exploring caregiving. Is caregiving on a continuum with only a change in site from home to institution? An individual who makes a placement decision resulting in formal care may describe it as a "benchmark-type" experience. Most certainly, transition into formal care caregiving

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involves negotiations among family, staff, and the health care organization. Clearer understanding of the concept of transition in relationship to the phenomenology of caregiving is needed. Research questions are presented which address the purpose of this study.

### **SUMMARY**

In summary, this qualitative research study involved two major pieces of data, one existing and needing analysis and the other remaining to be collected and analyzed. Spouses and adult children of Alzheimer's Disease care receivers form the study population. The purpose of this research is to generate knowledge about family caregivers' transition from caregiving at home to caregiving in the formal care setting. Specific focus will be placed on the issues faced in making the placement decisions, how caregiving in formal care differs from caregiving at home, and the caregiver's perception of the relationship that occurs between families and formal care.

# **Chapter 1**

## REVIEW OF THE LITERATURE

This chapter reviews five categories of relevant literature: (1) the elderly; (2) families and family caregiving; (3) dementia; (4) formal care; and (5) dementia, family caregivers, and formal care.

### THE ELDERLY

Between 1950 and 1980 the 65-plus population in the U.S. doubled in size, reaching 24.9 million. By the year 2000, this elderly population is projected to be 34.6 million persons and by 2030 will increase to 65.6 million (Ahmed and Smith, 1992). Also, by 2000, persons age 65+ will account for 13 percent of the total population and by 2030 they will rise; it is projected, to 21.8 percent (U.S. Bureau of the Census, 1988). Internal changes are another important factor in this growth rate. With the reduction of mortality from chronic diseases, life expectancy has increased proportionally for the older person. Thus the distribution of the aged population has shifted toward the "old-old" ages. This means between 1980 and 2020 the over age 85 group is expected to triple (Feinstein, Gornick and Greenberg, 1984). As life expectancy increases there is also an increase in the number of individuals who have long-term care needs, including medical as well as personal activities of daily living. Many individuals express concern about their prospective quality of life as they grow old. They are concerned about their health as it affects their status, the meaning of life, and most certainly their ability to avoid being burden on their family.

Knowing that the aged have become an increasing proportion of the overall dependency burden has important implications for society and the family. About 80 percent of these adults over 65 have adequate health to live independently, but there are approximately 20 percent, or three to four billion, who need outside help in order to manage (Springer and Brubaker, 1984). According to a report by U.S. Department of Health Education and Welfare (HEW), Federal Council on Aging, only 6.3 percent of the population under 70 is extremely impaired compared to 9.3 percent of those between 75 and 79 and 22.5 percent of those over 85 years. Townsend's recent study in Britain (cited in Bowers, 1987) indicated that three times as many severely impaired individuals are living at home as in all institutional settings combined. The 1975 National Center for Health Statistics report noted that families provide 80 percent of all home health care for older people (Horowitz, 1985a). Shanass (1979b) has projected that for every elderly individual in a nursing home there are two who are similarly disabled in the community being cared for by their families. For most individuals then, aging occurs in a family context. Of all the roles a family performs, perhaps its most seminal role involve care and nurturance (McGoldrick and Carter, 1982).

### FAMILIES AND FAMILY CAREGIVING

It has been argued that parent care has become a normative but stressful experience for individuals and families and that its nature, scope and consequences are not yet fully understood (Brody, 1985). A conservative estimate is that currently over five million people are involved in parent-care at any given time.

There are some demographic changes to consider in the discussion of family support. The declining fertility rate is profoundly affecting the availability of younger family members. This will clearly impact the kin network and its ability to provide support. The older population has also experienced changes in composition. The elderly relative today is likely to be a woman, a widow and very old (Treas, 1977). The old-old population in greatest need for care have children who are now young-old themselves. Women are increasingly working for pay outside the home. Economic changes have affected both the dependency of the elderly and the support the family can ensure. These shifts the

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### Chapter One: Review

demographic structure suggest that It will be the individuals who are engaged in their own aging processes who will be increasingly faced with caring for their parents (Robinson and Thurnher, 1979).

In 1979 a study of noninstitutionalized elderly (Stoller and Earl, 1983), found that spouses were the major source of help whether they were able to perform their AOL's or were impaired. Recent research by Barusch (1988) revealed spouse caregivers prefer to handle things themselves and are reluctant to seek or accept help. If the spouse was not present or able, adult daughters were the major source of support. For the demented patients, families are the primary caregivers until the 'burden' just gets to be too great (Zarit et al. 1980; Zarit, Todd and Zarit, 1986). These caregivers include wives and daughters predominantly although some husbands and sons are caregivers.

#### *Why Give Care*

It is important to look at why people become caregivers. Horowitz (1978) cited these family duty reasons: reciprocating for help received in the past, to gain a sense of personal satisfaction, to fill a void in their lives and to avoid nursing homes. In a study of caregiving satisfaction (Worcester and Quayhagen, 1983), over one-third of the study population indicated they assumed responsibility for giving care because the individual was part of the family. Other reasons included love and caring and the fact that there was no one else to give the care. Horowitz (1978) found that children who felt they were basically doing their duty did not mention any satisfaction or indicate successful adjustment to caretaking. However, children with a history of reciprocity and affective interaction adapted better to the caretaking. Thus many individuals do so because of a loving relationship while others simply feel an obligation to care for their elder family members.

An interesting study by Archbold (1982b) looked at caregiving roles. Most literature assumes one type of parent caring role. Through qualitative analysis of her data she suggests the roles of care provider, care manager and care transferrer. The roles are based on whether the services are identified and provided (provider), identified and managed (manager), or transferred to another individual (transferrer). "Parentcarers make changes in parentcaring roles based on ongoing assessments of the costs and benefits of caregiving". The four factors which influence the assumption of the care provider or care manager role include socioeconomic status (SES), housing arrangement, illness onset and past caregiving experience. SES had the most impact. Archbold (1982b) also noted that women who were working, especially in highly valued society positions, found a salient competing role to parentcaring. More providers (73 percent) shared housing with their parent than did managers (37.5 percent). Illness with a slow onset usually is associated with the provider role in contrast to the manager role that is associated with an acute onset. If the woman has had previous positive experiences with caregiving roles, it will facilitate her assuming the provider role. For these women this becomes very positive and personally valued.

#### *Caregiving Burden*

It is not marriage, parenthood, the climacteric or empty nest, but 'parent-caring' that is becoming a major source of life stress (Neugarten, 1979, p. 890). Family members usually assume a caregiving role without an understanding of what is involved or what the consequences of that long-term role are (Archbold, 1982a). Families must usually 'make it' through trial and error as there are as yet no training programs or classes to prepare for parent caregiving. The term, 'caregiver burden,' is now used widely to refer to the physical, psychological or emotional, social, and financial problems that can be experienced by family members caring for impaired older adults (George and Gwyther, 1986). Providing care for the elderly comes with a personal cost. In Archbold's study (1982b) the care providers identified experiences of decreased freedom, lack of privacy, constant daily irritation and guilt.

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The care managers identified invasions of personal time, career interruptions and financial burdens. In a study on family caregiving, Lerner, et al., (1991) explored the egocentric bias between siblings. A priority focus was on the costs and contributions in caregiving. While the caregiving siblings label their siblings as responsive as they themselves were in the caregiving process, they perceived them as contributing less, altering their caregiving with more freedom, feeling less satisfaction and being resistant to do more. Thus, even when adult children are receiving help from siblings, there are often issues of an interpersonal nature that contribute to the complexity of the caregiving role.

Another way to consider caregiver burden is to view it from the emotional and structural perspectives. There are many painful emotional reactions. Many researchers have found emotional stress ranked first before physical and financial (Cantor, 1983; Danis, 1978; Horowitz, 1978; Robinson and Thurnher, 1979). Mental health symptoms such as depression, anxiety, sleeplessness and feelings of helplessness are common. The individual often feels emotionally exhausted. Grief is a heavy burden which may be more devastating as a response to chronic illness than in the accompanying death (Springer and Brubaker, 1984). In some situations, stress can lead to passive neglect of the elderly being left alone, or active neglect of both a verbal and emotional nature.

In general, research on family caregiving supports or assumes a positive correlation between increased frailty or impairment of the elderly individual and caregiver stress (Bowers, 1987). Robinson and Thurnher (1979) reported a study which looked at late-life parent-child relationships. They found stress resulted in these relationships in two primary ways: first, through coping with perceived mental deterioration of the parent, and second, when the caretaking relationship was experienced as confining. This responsibility infringed on their lifestyle or if in retirement, their hoped-for lifestyle. An interesting sidelight, these individuals were not giving financial assistance to their parents who were using social security (SS), Medicare, and Medicaid.

The amount of strain a caregiver feels is closely tied to the bond he or she feels with the elderly individual (Cantor, 1983). The more caregivers feel that family members have a responsibility toward family and that family involvement is viewed as a positive value, the more likely they are to feel strain. 'Family members in the caretaker role of the patient have demonstrated role strain with those having close bonds exhibiting more perceived stress' (Ward, 1986, p. 47). Both Pearlin, Mullan, Sample and Skaff (1990) and Archbold, Stewart, Greenlick and Horvath (1990), have called our attention to the influence of the early caregiver-care receiver relationship upon the later caregiving situation.

While most of the research has focused upon the principal caregiver, there are many effects on the family system. The family is affected by interference with its lifestyle, life space, socialization, vacations, future plans, and income. The caregiver's time is diverted from other family members and there may be negative effects on his/her health (Brody, 1985). Danis (1978) reported the most frequent response his subjects gave when asked about the effect of their relative's illness concerned their restricted mobility and time away from their own families. Archbold (1982a) found marital conflicts arose. Sibling conflicts were often rekindled due to perceived inequities in contributions which then often stood in the way of any mutual cooperation.

As the review has captured, the stress, burden, and responsibilities are evident in caregiving of the 'frail' elderly at home. However, one crucial point remains. The nature of the care receiver's illness and functioning status greatly affects the reciprocity within the family caregiving system. An alert mind with a very ill body is a much different scenario than a strong body with minimal to no cognitive ability. Family caregivers to Alzheimer's individuals often comment that it is like a long funeral. The family member is often physically quite functional, but the mind can't remember and all the past history and shared memory is gone. The relationship is gone but the responsibility continues.

## DEMENTIA

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Symptoms of memory loss and a decrease in the ability to think and reason in adults are symptoms associated with the diagnosis of dementia. The cause of dementia of the Alzheimer's type is unknown but the progressive and irreversible brain damage is well documented. The patient often begins with gradual memory loss and ends as a completely dependent individual. This process may take anywhere from seven to 15 years (Lyman, 1989). The family caregivers find themselves with many new and often diffuse responsibilities. Somewhere on this caregiving continuum they begin the awesome task of diagnosis, trying to interact with the often confusing and hierarchical health care team. They must face the progressive changes in their ill family member and the demands in care these changes precipitate. They also face feelings these AD changes bring, such as denial of the illness, fear of injury with combativeness or abuse and embarrassment which often occurs with behavior changes.

Families often have trouble obtaining a correct diagnosis and then appropriate and helpful information relevant to their caregiving needs. In a study of Alzheimer's families' experiences, Chenoweth and Spencer (1986) found only 16 percent reported receiving specific help for dealing with personality changes and behavior problems. Fifty-four percent of the families reported the health team focused on the hopeless nature of the disease and if they did offer explanations, they were too brief. Inadequate understanding of Alzheimer's can aggravate the already overwhelming problems of caregiving (Dieckmann, Zarit, Zarit and Gatz, 1988). While a few families report the strengthening of family ties as they respond to the challenges of caregiving with an Alzheimer's patient, many families find the need for constant physical care and/or supervision a major problem (Chenoweth and Spencer, 1986). Rabins, Mace and Lucas (1982) reported chronic fatigue, depression and anger in AD caregivers. It is also common to hear of feelings of isolation as they are unable to leave the house or friends stop visiting. In a study of different caregiver types, Quayhagen and Quayhagen (1988) found wife caregivers more stressed by frequent disruptive (dangerous and embarrassing) acts than husband or offspring caregivers. The offspring were most stressed by having to bathe their parent and the parent's inability to stay alone. Repetitive questions from the AD care receiver were stressful for all groups. As the disease unpredictably progresses, the care receiver's behavior typically changes, resulting in increased likelihood of assaultive behaviors, wandering and incontinence. With such changes, the caregivers must constantly modify their plans and adjust to new problems. Yet the national profile confirms a low use of formal care by caregivers (Stone, Cafferata and Sangl 1987). In a sample of 209 caregivers, Colerick and George (1986) found caregiver characteristics and caregiver well-being were more important predictors of institutionalization than were patient characteristics. Probability of institutionalization was more than doubled if the caregiver used psychotropic drugs while two factors significantly reduced the probability; 1) the relationship of the caregiver and care receiver and 2) the caregiver's need for caregiving assistance. Spouses are the last to relinquish care often due to their belief in the central role the patient plays in their life. This gives them internal empowerment as a caregiver. It is important to note in this discussion that female patients are at much greater risk for institutionalization. Greene and Monahan (1987) studied the effects of caregiver support and education on institutionalization of the care receiver. One pertinent finding is, while support and education can decrease the likelihood of placement, Alzheimer's was the only disease to predict formal care. Regardless of the cause of placement, it is widely supported that formal care is viewed as a last resort.

## FORMAL CARE

One of the most unhappy times in the life of any human being comes when he must make the decision to institutionalize a parent (Oath, 1972, p. 25). In the past, placement of a loved one in a nursing home was viewed by society as neglectful and families themselves felt a sense of failure. Even though people continue to hold negative stereotypes, the research conducted in the last decade does not

provide support for this viewpoint. For a detailed survey of formal institutions see reviews by Horowitz (1985a).

Nowadays, entry of a family member into formal care can mean a shift of responsibilities, not a loss of the relationship. This change in site of caregiving does exact a price for family members. The disruption of the family relationships and the obvious change in the physical environment can contribute to a great sense of loss and grief (Greenfield, 1984). Tobin and Kulys (1981) have reported patients with feelings of abandonment and family members with feelings of guilt. The attitudes of family members can greatly influence the positive adjustment to a nursing home. Strong family relationships can continue and Miller (1986) notes affection may even increase. Shuttlesworth et al. (1982) have noted the quality of care in nursing homes appears to be better for those patients whose family members remain involved.

Involvement, in nursing home language, often means the assignment or delegation of "tasks." Litwak (1981), and Litwak, Messeri and Silverstein (1990) have proposed a "theory of shared functions" whereby staff would be primarily responsible for the technical tasks and family would handle nontechnical tasks. While in actuality, the technical tasks appear to have been assigned to formal care staff, Shuttlesworth et al. (1982) found great ambiguity between families and institutions in the responsibility for nontechnical tasks. A critical aspect of formal care centers around the staff-family relationship. Both families and staff have learning needs. Hirst and Metcalf (1986) in a study of families with dementia patients found families needed and desired information around the disease process, information to help them know their place within the formal care hierarchy and how to deal with their emotional responses. Nurses were also discovered to have learning needs in the areas of cognitive knowledge about the aging process, pathophysiology, assessment of the dementia patient and finally, knowledge of family dynamics. Brower (1981) would add that the attitude of the nurse has a critical influence on the type of care he/she delivers. It is the view of Bowers (1987, 1988) that effective collaboration between staff and families comes from a shared perspective and understanding of the invisible work of caregiving rather than a splitting of tasks.

Finally, policies often influence the level of care and behavior of staff. In a study of facility policies and family relationships, Montgomery (1982) concluded that policies that view family members as clients rather than as servants will have the most positive influence on family relationships.

### DEMENTIA, FAMILY CAREGIVERS AND FORMAL CARE

In discussions of institutions and caregiving, the family indeed, often remains the 'forgotten client' Pratt et al. (1987b), in exploring this notion, has highlighted the often older age and at-risk health status of caregivers to dementia patients. This becomes an important issue if caregiving activity has the potential to contribute to the overall health of a caregiving individual and provide growth producing experiences for not only the individual but the family as well.

Families who have been providing home care to a relative with dementia are signaling the formal care institution of an established commitment. These families often experience a strong desire to continue home care but as research by Worcester and Quayhagen (1983) has documented, the potential for nursing home admission increases as the psychological and behavioral problems of the care receiver increase. Family attitudes toward institutions are not commonly assessed at the time of transition to formal care but Deimling and Poulshock (1985) have identified their significance in family decision making. If caregiving is on a continuum, then increased awareness of the influence of attitude toward formal care for families of dementia patients will contribute to our better understanding when the shift in the caregiving site occurs. There is no way to project the course of Alzheimer's Disease,

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and thus, the demands and burdens for caregivers vary greatly over time. Just as individuals and families differ in their desire and ability to provide caregiving, so do their responsibilities and resources. Though one is not able to project a picture of each individual caregiver, through research there emerges a description of caregivers in general.

Recent studies have given us insights into the special risk for negative outcomes that face families who care for their family members with Alzheimer's Disease (Gwyther and George, 1986). In a study comparing family caregivers of dementia patients to a community sample of non-caregivers, George and Gwyther (1986) found large differences in mental health indices. The caregivers had nearly three times as many stress symptoms, had lower levels of life satisfaction and a substantially higher rate of use of psychotropic drugs. They also reported less participation in social activities except attendance at church. For example, the community sample reported twice as much time spent in relaxation activities. Pratt et al. (1987b) in a study comparing Alzheimer's caregivers at home to those in formal care found the Institutionalized residents' mental status was significantly more likely to be rated as poor by family caregivers. Those caregiving in institutions were not only more likely to rate their health status as fair to poor but they were also significantly more likely to note the negative effect of caregiving upon their health status. Their issues of burdens were significantly more focused on concerns around finances to cover care, worrying about being able to continue in a caregiving role yet desiring to leave the caregiving to others and finally the sense they should be doing more. These findings certainly describe feelings of guilt but one also notes a sense of ambivalence. Is it possible that with their family member becoming more severely cognitively impaired and their personal health status in jeopardy, these family caregivers still feel a sense of failure upon turning to formal care? Although formal care may solve some of the family's problems, being on the rollercoaster associated with dementia caregiving, new needs will most certainly surface.

In a recent study of family caregivers to Alzheimer's patients, Morgan (1988) reported not only do caregivers wait until almost the last minute to institutionalize, feeling guilt and a sense of failure for doing so but afterwards they express guilt for having waited so long to place their family member. Caregivers also have been known to try a return to home care if a little stability or slight improvement is noted in their family member. They reported little success with this coping strategy. Other caregivers shared their approach of moving between one formal care site and another, always in search of that elusive something.

Family caregivers -- when we hear these words, what image comes to mind? Too often no distinction is made in the type of caregiver, yet this is an extremely significant variable in the formula of care for the dementia patient. Another point to reflect upon in comparing types of caregivers, is that the comparisons presented are often an aggregate rather than an individual profile.

It is difficult to find research that focuses upon spouse and adult children caregivers for institutionalized dementia patients. In a study by George and Gwyther (1986) comparing caregivers of dementia patients to a random community sample, 41 percent of the caregivers were providing care to an institutionalized family member. While the lowest level of well being was noted in at home caregivers, the caregivers to institutionalized patients continued to experience mental health and social participation problems. The data did not allow a comparison of the spouse and adult children caregivers of institutionalized patients.

However, in their overall comparison of spouse and adult children, the spouse caregivers exhibited lower levels of well being in the dimensions of physical health, mental health, financial resources and social participation than the adult child caregivers. These findings contrast with Robinson (1983) and Zarit et al. (1980) who found no significant differences in caregiving burden between spouses and adult child caregivers. The later studies, however, did not include caregivers to the institutionalized

family member.

Husbands and wives caregiving for dementia patients at home may experience similar degrees of burden but the female reports more symptoms of depression (Fitting, Rabins, Lucas and Eastham, 1986). More women than men reported a deterioration in their marital relationship but over 25 percent of the men stated an improved relationship with their wife after they assumed the caregiving role. It is important to explore the effect of institutionalization on depression and this spousal relationship. If depression results from a sense of hopelessness or powerlessness that accompanies dementia caregiving, then these spouses may find a different role after institutionalization. Men, who are often at loose ends upon retirement, may find that spouse caregiving provides them with responsibilities or a new 'job.' Institutionalization will impact this caregiving experience for the male caregiver. These issues reflect on the importance for us to explore the subjective experiences of husband and wife caregivers which will not be captured by objective measures. Much remains to be discovered about spouses and adult child caregivers, dementia and institutions.

In exploring gender differences of adult child caregivers it was previously documented that daughters most often assume the caregiving role. Horowitz (1985b), in a study of adult children who were primary caregivers to their frail elderly parents found when sons did take on this role they tended to provide less extensive support, were less likely to help with hands-on type assistance, and had less stressful caregiving experiences independent of their involvement. Of significance, over 90 percent of both sons and daughters cited providing their parents with emotional support was their most common role. The common behaviors included talking to the parent and giving advice.

If institutionalization occurs, the relationship between the adult child and the parent can be continued or even enhanced. This strengthening of family relationships results from decreased strains on the family due to parents' acute needs, often the physical and mental improvement of the parent and the involvement of the parent with other residents in the institution (Smith and Bengtson, 1979). These parent-child interactions imply a reciprocity not likely for caregivers of Alzheimer's patients where memory has failed and behavior is very unpredictable. The influence of dementia should be integrated into future caregiving research on gender differences.

Institutionalization of a parent is indeed a traumatic event but this experience may provide a family with the opportunity for learning and growth (Smith and Bengtson, 1979). Caring for an elderly parent or spouse may be considered a developmental task. Spouse caregivers who achieve integrity after admitting their spouse to formal care must accept the past as it was, respond to the present with acceptance, and recognize that their current involvement will be controlled by the policies and procedures of the formal care facility (Brubaker, 1986). For both types of caregivers, the work of transitioning to formal care is influenced by the response of the formal care facility. Finally, the quality of nursing care has been shown to improve with greater family involvement (Dobrof, 1981; Harel, 1981). There is no dispute that families remain the 'forgotten client' as identified by Pratt (1987b).

### *Division of Labor and Formal Care*

In a major policy-oriented work, Litwok (1985) analyzed the basic differences between primary groups and formal organizations. Because of their basic structures, primary groups, such as the family, can best manage unpredictable events and nonuniform tasks with many contingencies. By contrast, formal organizations can best manage the uniform services often referred to as technical tasks or tasks requiring technical knowledge and expertise. The key variable is the amount of technical knowledge required. If technical expertise is not necessary, the lower cost, increased time available, greater flexibility and higher level of internalized motivation of the individuals make the family particularly appropriate for caregiving tasks. If however, technical expertise is required, the structure of the formal

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organization is cheaper, faster, more flexible and able to provide more motivated individuals (Litwak, et al., 1990). In other words, the structure of the group should match the structure of the task, thus the primary group matches tasks not requiring technical knowledge and the formal organization matches technical tasks. This does not, however, mean that family and staff should perform separate tasks. Litwak et al. (1990) note that there is a functional division of labor between the roles played by staff and family, and the highest quality of care requires contributions from both of these two sources of caregiving.

Much of the past discussion of families and institutions has been embedded in the language of 'tasks.' First, they were discussed, then identified and finally attempts were made to delegate tasks, often technical ones, to staff and non-technical ones to family or as a shared function. However, Albert (1991) in an exploration of dimensions of caregiving, noted that typologies for categorizing caregiving tasks reflect the perspective of the service need rather than that of the caregiver's understanding of the domain. Ambiguity in the subdivision of these tasks may hinder the staff's ability to integrate families into patient care (Rubin and Shuttlesworth, 1983). In their 1983 study, Rubin and Shuttlesworth identified five broad problem categories: personalizing care; monitoring and ensuring the provision of care; meeting clothing needs; grooming and providing reading materials. Meaningful family involvement resulted from agreement in task assignments but these assignments must often be reviewed and encouraged by both staff and families.

Most research that has looked at relations between family caregivers and paid staff conceptualizes this issue in terms of the assignment or delegation of tasks. Studies in this tradition use quantitative checklists to gather ratings from both staff and family concerning who should do various tasks. When family or staff over or underestimate either their own involvement and responsibilities or those of the other role, stress and problems are likely to occur. More recently, Schwartz and Vogel (1990) found significant agreement between these groups. In areas such as 'personal care' and 'activities,' however, the responsibility was still assumed by staff, even though the family was willing to share in these tasks. Thus a major theme in the literature to date has been the appropriate division of labor between family and staff, assessed in terms of which task should be assigned to which caregivers.

Bowers (1987, 1988) has provided the most prominent critique of this task assignment approach based on her qualitative investigation of the family's caregiving experiences. Her intensive interviews with family caregivers concerning their experiences and feelings, demonstrated the limits of a task-assignment approach. Family caregivers did not relate their caregiving in terms of tasks but rather described their care by its purpose. Specifically, caregivers for institutionalized family members do not want their family member to feel like a burden or nuisance for staff (Bowers, 1988). At a broader level, these family caregivers believed that the most important purpose of their involvement in formal care was to preserve the older individual's identity. Families expected staff to provide care in a way that was not only high in technical expertise, but also sensitive, nurturant and individualized in many ways. The staff's ability to deliver care that met these 'emotional needs' depended on contacts with the family. Family perceptions of good quality care were thus based on a collaborative process involving shared perspective and understanding of the work of caregiving rather than an assignment of separate tasks.

A discussion of family caregiving which incorporates relationships, interactions, and reciprocity must also recognize the ethical concerns these situations create. Pratt et al. (1987a) conducted a content analysis identifying ethical concerns in an open-ended question asking respondents to share any additional information that would help the researchers understand their caregiving experiences. The sample included spouses and adult children in both home and formal care settings. The most frequent (42 percent) concern was family obligations in caregiving followed by conflicts between caregiving and other commitments (29 percent), ethics in financing health care for dementia patients (13

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percent), standards of professional and family care (13 percent) and the patients' roles or responsibilities in planning care (3 percent). These moral and ethical dilemmas impact not only the caregivers, care receivers and their families but the health care system and society as well.

Thus, as the review of literature has highlighted, family caregiving by its nature, is a private, sometimes painful and often difficult area to study. Research must be designed to address the gaps or increase the knowledge base. However, sensitivity must be shown to families at this vulnerable time in their life.

### *Summary*

Literature was reviewed from several perspectives and organized into five areas: (1) the elderly; (2) families and family caregiving; (3) dementia; (4) formal care; and (5) dementia, family caregiving, and formal care. It is evident that families do become caregivers to their elderly family member. In doing so, they experience burden and stress that affect their health and well-being. Dementia, in its often gradual and unpredictable course, carries family members into caregiving which often ends in institutionalization. This shift in caregiving site is often the caregiver's last resort and his/her new role is confusing at best. Minimal research has been devoted to family caregiving to dementia patients in formal care. Special attention should be directed to the distinctive experiences of caregiving spouses and adult children as they transition into formal care.

# Chapter 2

## REACHING THE END: DECISIONS

Although there have been several discoveries and insights into the AD process, the caregiving

family continues to encounter challenges as the disease process leaves its effects upon the family member. They face many unknowns and decision points in their course of caregiving. They must relate and respond to not only the ill family member, but also factor in extended family members, the health care system, support resources, economic issues, and social-legal guidelines. Somehow, they find the time and energy for these constantly changing demands and make decisions as to what takes priority at this caregiving moment. This life of the caregiver has been well documented in such popular publications such as The 36 Hour Day (Mace and Rabins, 1981). However, there comes a time when, influenced by this around the clock toil, the caregivers perceive the outcome as no longer functional and responsible. Recognizing a turning point, the caregiver then enters into a decision process that results in placement of the care receiver in formal care. This move involves the transition from caregiving at home to caregiving in formal care which results not only in an environmental change for the care receiver but a role shift for the caregiver.

Transition is the conceptual framework underlying this research project. If another name for transition is change, then the changes in the caregiving role that these caregivers are experiencing at this time of move to formal placement constitutes a transition.

Bridges' (1980) transition framework is organized and practical but it hasn't been applied to the caregiving situation and thus there are reasons, as outlined earlier, to explore its fit. There will be an attempt to use it as a conceptual framework and one of the goals at the conclusion of this project will be to assess how appropriate a conceptual framework it truly is. Clearly, Bridges' 1980 model is an adequate organizing framework for presenting the material but is it a conceptually rich framework which helps us better understand transition to formal caregiving.

As detailed earlier, Bridges (1980) identified three passages in the transition process; endings, the neutral zone, and the new beginnings. This first passage, defined as endings, is a time one finds themselves letting go of something. There is no set order in how endings happen or any commonality in response between individuals who experience a similar transition. Often endings are perceived with something going wrong. Bridges (1980) notes of endings, 'They are ordeals, and sometimes they challenge so basically our sense of who we are that we believe they will be the end of us. Even though the change this ending brings may be either unforeseen or undesired, it must be dealt with in order to move on with what comes next.

Although a decision may signal the end of one thing and the beginning of another, in these AD caregiving situations, that is not the case. While the site has changed, a caregiving role continues. Thus, in the decision for formal care placement there is simultaneously both termination and a continuation. It is within this understanding that the following three chapters are organized within a data oriented presentation. The focus of this section is on what happens around making the decision, and what it's like, In the home, at the end. The next section, addresses what happens in the move to formal care and to caregivers familiar with caregiving at home who are now trying to adjust to continuing caregiving in formal care. The last section focuses on the caregiver's adaptation to the new way of life and development of the relationship with the staff who are in essence now the primary caregivers. Thus the findings will be organized into a data oriented presentation around three issues: endings-decisions, placement and the new beginning.

The focus of this section is centered on what happens around making the placement decision, the decisions that end the ability to care-give at home and to start the next caregiving role. It is important to note that decision-making is initiated in the ending phase. To decide has all kinds of future implications that affect how a decision gets made, when it gets made and what that end is like.

As the family members lived their caregivers role, they became aware of the many decisions they made along the way. However, they have also discovered that not to decide is to decide. On occasion, they made a decision in advance with anticipation and foresight, and yet, when they got there they chose to discard that decision through circumstances or they realized their thinking was changed. They may have thought something wouldn't be a problem only to find it is more than they could bear. They

could anticipate a certain situation would be the straw that would break their back and when they got to that point they were a lot stronger than they thought they would be. Therefore, many of these decisions do not result in the transition to formal care. It will be useful to be able to identify key issues and their influence upon the families' struggle with the difficult turning points and decisions in their caregiving roles.

### FINDINGS

The findings in this section have relied mostly on analysis of the individual interviews. Although the initial purpose, as outlined above, was to organize the findings into the three identified areas, an important finding emerged. *Family* and *surviving* were revealed by the family caregivers as two themes that were of consistent and intense influence throughout the entire process from early caregiving, through transition, and into the adjustment period after placement in formal care. Therefore, they are appropriately integrated into the discussion of the findings in Chapter VII.

The family members in this study identified five specific themes that were crucial in their decision to place their care receiver in formal care. There was no specific theme, by itself, that caused the move; however, family members related an additive influence when changes began to mount. The five themes, in order of their influence as identified by family members include: **event, health care system, caregiver-care receiver relationship, support, and options and availability**. The order of influence was judged by the amount of time devoted to the topics in the interview and caregivers' perceptions of the importance in their caregiving decisions.

#### Event

To what extent was the decision driven by events? The easiest way to imagine this happening is through a crisis-type event. These, in fact, proved to be relatively rare. But there were a number of other things that caregivers spoke of as events that were the turning point in their decision-making. Often these were related to the progression of AD. To understand why these kinds of events were such a turning point needs to be seen against what caregivers mentioned more often than crises, a *sense of exhaustion*. As exhausted as these caregivers became, it does not take much of an event to become a turning point.

The obvious kind of crisis event one would think of is a situation that immediately disables either the care receiver or the caregiver. If the care receiver is involved, there is most likely a quick move to acute care and then a shift to a more continual level of care. If the crisis takes the caregiver out of the picture, formal care is the common replacement. These kind of crises were relatively rare (Three of the ten interviewed caregivers experienced health crises, two in the care receiver and one in a caregiver.) The care receivers were much more likely to suffer the physical illness or need for immediate hospitalization, however, when the caregiver did suddenly become ill, the situation became complex and the return to the caregiver role was extremely uncertain.

As the disease process took its toll on the caregiver, the sleepless nights and frequent need to reshuffle caregiving priorities resulted in extreme burnout. The one commonality that affected spouse and adult children and male as well as female caregivers was *exhaustion*, both physical and emotional. It is important that nine of the ten caregivers interviewed mentioned their physical exhaustion and three of these nine also spoke directly and poignantly of their emotional exhaustion. However, it must be stressed these numbers over-simplify the situation and in no way capture the complexity of this issue. As an example, the two adult children, who tried to resume home caregiving after a care

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receiver's physical crisis, were able to continue only briefly. It was as if their short time without the care receiver at home let them see how exhausted they had become.

### Turning Points

The turning points that were consistently and intensely described by caregivers in the move to formal care included *issues of safety, dealing with incontinence* and the *AD progression*. Interestingly, safety was identified more often by the female spouse caregivers and incontinence by male spouse caregivers. Caregivers often spoke of comparing the care receivers' needs versus their ability to deliver the care. In the home caregiving environment there was always an issue of care receiver independence versus *safety*. As the disease progressed, the safety issue assumed increasing importance and priority. Adult children struggled most with this issue as they had always related to their parent as an independent adult. It was as if, by making the decision to keep the parent safe by decreasing his or her independence through placement, the children were the cause of their parent's loss. It was a difficult adult child caregiving dilemma. A daughter in a focus group shared:

It just kind of gets to the point where you have to come to that conclusion for their own good you have to do this. In our case I think we let her have her independence as long as we felt she could have it. Maybe longer than she should have, but it did work out all right, too, to let her have that.

Dealing with *incontinence* was often the first reason presented in the caregiver's placement description:

Well, I think what really brought the thing to a head was her incontinence. A full bladder, bowel just got to be- I was up all night and, not all night, I was up late at night and things Just got, oh I don't know. (Husband)

She had to go to the bathroom and it was in five minutes then she started again and 'I've got to go to the bathroom' ..... That was it, so she had to go and then she went out again but many times she confused the bathroom with the front room .... here she was sitting on that little table, you see over there, that golden leaf table. She was sitting there and one time she confused right in the middle of the carpet because she didn't make it. Actually she intended to she thought the toilet was there and wanted to sit down, you know. (Husband)

Male spouse caregivers consistently detailed the great challenges they faced in an attempt to deal with incontinence, bathing and dressing their wives. As the actual physical caregiving demands increased other challenges emerged. Families shared concerns about, not only their actual physical issues of delivering personal care, but also how they struggled greatly with a lack of knowledge to make clinical judgments in order to deliver professional care 24 hours daily.

The findings would not be complete without the acknowledgement of the influence of the AD progression upon the placement decision. Family caregivers are often able to deal with dressing, redressing and early memory losses; however, when the serious behavior changes begin, the demands on the caregiving role intensify. The caregivers realize the care receiver is requiring a level of AD care they can no longer provide. This is captured in the following focus group dialogue from a daughter:

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But we have, we have tried everything first, and like I said I think there comes a time when you realize that they Just need more care than you can give them. They need professional care....

For the caregivers who experienced an AD crisis, It was not so much that the AD event was making a difference but the ongoing aspects of caregiving that were somehow shading into a new series of events that were the end. It was more an outcome of caregiving and an outcome of the disease process rather than a direct cause of the decision-making.

In summary, although identified as an event, there was usually no particular crisis that precluded any other option and forced a decision. There was a combination of a predisposing factor of exhaustion matched with a turning point event such as issues of care receiver safety, incontinence, and AD progression. There is not a clear way these events influence decision making. In other words, caregivers will continue to work through that 36-hour day and fight off the placement until some turning point event changes their way of thinking around the decision issue. As the caregivers' struggle with these decisions this may be the time they have to consider reaching out to professionals for help.

### **Health Care System (HCS)**

Although HCS was second in their order of importance, the caregivers were more clear in their descriptions of this theme. In reality, caregivers do not get to the turning point toward formal care without previous encounters with the health care system. In fact, all caregivers had a HCS story. In essence, why the "event" steered things the way it did often had to do with their prior contact with the health care system. Past interactions and perceptions surround the importance they place on the HCS as they approach decisions. Families were clear on this issue, the HCS was viewed as either positive or negative. There was virtually no in-between. When families talked about the HCS in positive terms, they first shared examples of how it helped influence the decision in a way they felt good about. They might identify a particular service that was helpful at a particular time or a suggestion for a resource that, when they followed up, proved useful. In essence, this often allowed them to decide to continue with caregiving at home for a while longer.

Second, family members spoke of the HCS as providing direct help for themselves as the caregiver. When they shared this information, it took on a personal tone and was often identified within the framework of an interaction or relationship. Even if the decision needed to favor the move to formal care, they gave clues to feeling supported, respected, and cared about as individuals themselves. The following is a quote from a daughter caring for her mother:

I don't know where I'd been without the doctor . . . I would call her anytime and she would call me back and never be . . . I was never even charged for it. She just worked with me, you know. When Mom went into the nursing home, I sent her a great big bouquet of flowers and said, 'Thank you for being a wonderful doctor.' Because I would have been lost without her.

The majority of the HCS discussion, however, revealed negative experiences and perceptions. The major themes included misdiagnosis, medication mismanagement, indifference, and professionals with limited AD knowledge base. These experiences played out in two major ways, they prolonged the decision to access formal care and once the decision for placement was made, they influenced the families' initial ability to develop a level of trust within the formal care facility. Families' perceptions revealed much sensitivity in their interactions with the HCS as noted in the examples that follow:

Well within hours of the operation (hip), they didn't watch her and she got out of bed

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somehow, dragging all that packing and her catheter and everything else and then fell right out of bed so then she had to have another operation on the other hip. (Son)

We were really quite unhappy with the emergency situation there at X hospital because not only did it keep us waiting and before we went in, but then when we did get in, we sat there again because they had other emergency .... So were it was like we were there like five or six hours just to get the arm set. And I knew she'd fallen backwards. But they never x-rayed anything except her arm and he fixed the arm and then sent us home .... that even getting her up from the bed to the portable potty she would just scream she was in so much pain We talked to the doctor and she said, 'If you can bring her in to see me in my office, then we'll go from there.' So we did this and she said, 'Lets put her into the hospital,' because she had fractures of the vertebrae. (Daughter)

And then the second time they sent her home with the wrong medication for her, she has seizures. Her seizure medication wasn't correct. I asked the nurse, I said, "How come she's going home on such a low seizure medication?" .... I said, "Gee, that doesn't sound right.' But I thought I'm no medical person, but it just didn't sound right. So we took her home on three a day and within a week, she had one of her major seizures . . . So they called the ambulance and we took her to the hospital . . . They called me at work and said, 'Can you come down?' and I talked to the social worker and she said, "I think this is the time where it will be- we can work it to get your mom into a nursing home." (Daughter)

And I never dreamed that this one doctor, when he, he put him on a drug holiday, took away all, everything, which I understand is of useful, but the point is that X (husband), has Parkinson's too. And he took away all of his meds. Well, in three or four days, he couldn't walk, couldn't get out of bed and so I didn't know that. Suddenly the nursing home called me and told me that he was, the condition that he was in and that the doctor had agreed to put him back on his med. So at that point, this is about two weeks after he'd been there, at that point, I discovered that everything else was gone too you know. And I was really kind of angry and so I just started raising heck with (laugh) everybody. (Wife)

As obvious in the information shared by families, if the health care system in general was not the best place to turn for sensitive and consistent help, families must develop other avenues to turn to in their caregiving journey.

### Caregiver-Care Receiver Relationship

In the earliest stages of the caregiving relationship, the care receivers are in essence a source of the efforts that are necessary to meet the Job. Initially they have periods of independence that are sufficient for meeting their needs or they access their necessary support network. Slowly, and over time, the family member who was initially providing occasional support becomes the caregiver and there is a major shift in the responsibility. Caregivers described strong influences from the **previous caregiver-care receiver relationship**, the **known health care wishes** of the care receiver, and knowledge of **previous caregiving experiences** by the care receiver.

The **previous relationship** between these two individuals exerts a powerful influence on the

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continuing caregiving-care receiving relationship. Family members identified two directions of influence: one, within the actual one-on-one relationship, and two, within the influence on caregiving decisions. Caregiver perceptions of how they as mother-daughter or husband-wife interacted in the past provided insight into the current caregiving interactions. Three mother-daughter pairs are presented for comparison of this point:

### I.

We will pay for a milkshake or get her a pop or some kind of a treat and sit there and visit. I sit there and talk to her when she doesn't make any sense at all, but I pretend like we are having a nice visit and so on and so forth .... I brush her hair and put combs in it, try to keep it out of her face. I have arranged for a beautician to groom her hair like on every other Wednesday or whatever so that she, because I'm sure she remembers how good that feels and that makes her feel better .... I Just hug her and get her and take her outside because she enjoys that. . . So my going out there so often is because of the closeness I feel with her. Since I'm the only family that's here I want to give her as many hugs as I can, make her feel like she still has family. I'm doing it for her and not really for the home or can help the home in any way. It's just my closeness for her.

### ii.

She would always behave for me. I think it was because I was the only daughter and I'd always been very close to my mother growing up .... I knew my mother very, very, very well. I knew what she liked and I knew what she didn't like. ... We Just sort of knew each other very closely.

### iii.

I wheel her out to the courtyard. They have a beautiful courtyard and nobody uses it, at least when I'm there. And then we have absolute privacy. And I do her nails or I sing to her because I've been taking voice lessons. So I sing to her or read poetry because she always loved poetry. . . And so then I'd read her these little poems that she was just-were dear to her that she'd memorized in her childhood .... And people just don't understand. But for me, it's almost like this is one of the specialist times for us because, well, quite honestly, my mother was a very unhappy person. She was bitter and sullen and ah, she was kind of disapproving in general of . . . including me. Especially me, or at least I felt it maybe more than other people (laugh), she can't tell me now that I'm doing stuff wrong. All she can be is just a sweet little bundle of love you know, and I can hug her and kiss her and tell I love her and all this stuff that I always wanted to do. It's sort of like I'm making up for lost time. And I'm trying to manage something that was broken.

Another important influence of past relationships is in its ability to affect the caregiving decisions. If the caregiving pair had an open, trusting communication style, then caregiving issues were freely raised and a variety of options were explored. If, however, the family member had a closed or mistrustful relationship, not only were options not explored but significant caregiving issues were never raised for discussion, let alone exploration.

Often the care receiver had shared his/her wishes on specific forms of treatment, placement in a nursing home and/or the right to life or death procedures. Families struggled greatly with these issues. Although they realized the care receivers lack of recognition of the actual caregiving environment or situations, they struggled with 'knowing' as they made the painful placement decision. Caregivers implied the decisions would most likely have remained the same but this specific issue greatly increased their caregiving stress.

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Well, she is dead in a way, in many respects, there is a death that's taken place and it's sort of like dealing with a residue and being respectful as you can. It's beyond the point I would want for myself. It's beyond the point where she would have wanted for herself; she had no choice in the matter. (Son)

He always had a thing about going to any, you know, he had this idea that, 'I go to a nursing home, that's the final thing. That's the end.' And he would say this too. Well, (laugh) guilty, but very relieved at the same time because I just felt like I was at the end of my rope. I was nervous, high-strung, and not good for him, you know. (Wife)

Because this isn't any kind of a life that he's leading and you know, because I know he wouldn't want to live like this or if he was to have a heart attack or whatever and die, maybe that's all for the best because why drag on like this. (Wife)

**Past family caregiving experiences** had the ability to influence the present caregiving situation. It was not unusual that the care receiver had been a caregiver to a parent or extended family member in their past. Aware of the family history, the caregiver made the decision they should carry on with that caregiving style. Stressors often occurred as the earlier generation, the care receiver, set a standard under different circumstances that this caregiver could not live up to in the present.

One might expect to find that an adult child who has accepted this caregiving role in the family may also have a previous caregiving history. However, the magnitude of the findings in this study were surprising. Three of the four adult children had also provided caregiving at home for their other parent. What they shared was not their disappointment at the loss of a parent, as they already had that experience, but their inability to succeed this time in their caregiving at home. Because of this history, these caregivers found themselves deciding to delay placement until the last moment and perceived a much greater level of exhaustion, emotional stress and sense of failure with placement.

It wasn't something I had ever wanted. I had intended to take care of her. My father died at home and that's ideal. He didn't have to go to a hospital or a nursing home. At the end he had a lot of things. I was putting formula down his tube and having to put that in and out and forth. We managed, but at that time I was 10 years younger too and you notice it. (Daughter)

I felt like I was committing her to a death camp, because, and X (husband) reassured me that it wasn't that at all. She was being placed in a facility where she'd get the kind of skilled care that she needed. But I really felt like I was committing her to something worse. (Daughter)

In summary, the previous caregiver-care receiver relationships have the power to exert influence upon the present caregiving situations. Although, because of a shared history, caregivers desire to continue in a home caregiving role they often find themselves facing increased stress with these difficult decisions.

## Support

Early in their caregiving role families find themselves needing to turn to others for help, assistance and advice. As they log in the many weeks, months, and years of caregiving they became quite articulate as to what works best for them. Caregivers highlighted three sources of resources to meet

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the challenges they faced: (1) **informal**, (2) **formal**, and (3) **self**.

In their **informal sources**, families identified the positive influence of the extended family network. Some of the specific examples included actual caregiving help with the care receiver, providing words of encouragement and support, and affirming decisions made by the caregiver. When family members got involved in the actual caregiving situation, it provided not only a brief relief for the caregiver but a bonus benefit in the family members' better understanding of the care receiver's decline and what the caregiver was experiencing on a daily basis. Thus these family members were often able to be more understanding of the formal care decision.

I think contacting your family and getting everybody to agree, you know, they don't pay for it but keeping them aware of what's going on, what things are really like. I used to get them once in a while to come over and give me a few hours respite. And that was more valuable—what they learned here taking care of him was more valuable than any time I got away. The girls used to trade off Sundays. Sunday afternoon was mom's afternoon out and they (laugh) they learned a few things. (Wife)

Some caregivers noted an interesting contrast in their current friend network. By this time in the AD process, their friends have mostly disappeared. A male spouse shared in a focus group discussion:

The worst part of what is going to happen is the phone stopped ringing. Friends no longer call. This is the worst part because you see we are pretty much aware that with Alzheimers, actually you suffer more. You suffer more. She is dying inch by inch practically. You see it over a period of time. And this is where you need the most support.

The drastic changes in the care receiver's behaviors have made social interactions difficult and friends have stopped coming or are at least less available now.

And when they came in, they came this way towards X (husband). He was sitting like you are, he would have been facing them. M. and her sister both spoke to me, 'how are you?' and so on and so forth. They looked at X and you know they didn't know what to do. They walked off .... Years ago, they would have patted his shoulder, and said 'how are you?', 'good to see you' and probably would have given him a hug, but they walked off. (Wife)

But not many friends, you know. They bail out fast. (Son)

The caregivers' **formal supports** included specific individuals within the health care system, home health services, respite resources, and support groups. It is important to note the contrast here between the HSC as a general agency which was alluded to earlier and professional individuals within the system who really made a difference for the caregivers and their decisions. By far, the most frequently mentioned helpful individual around transition information was a social worker. One might be inclined to think that is their job. That was exactly the caregivers' point. According to these families, they were successful in providing a needed and respected level of support at a critical time. On a rare occasion the caregiver had a supportive relationship with a physician and was not hesitant to turn to him/her for help and guidance at the time of transition.

For those families who found the physical care becoming too demanding, **home health services** were cited as a resource that helped them continue to maintain for a while longer. This quote by an adult daughter demonstrates the point:

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And so we decided, well, we would find people to come into the home that were willing to do it on a 24-hour basis for less money. So that's how we started the 24-hour caregiving, seven days a week. That was to take some of the pressure off of me and also to free up some of my evenings where I wouldn't be quite so involved. (Daughter)

However, later in her discussion she outlined the amount of time and energy it took to find the right person for her mother and this job. So, this support also came with an energy cost and in the end this was factored into the decision for placement.

Often families are at the burnout point from being up day and night or needing to work and having to caregive all night. For these families it isn't so much the physical care but their level of exhaustion. Respite care often provided a resource that worked to extend their caregiving. While upon reflection respite was recognized as an important support, the decision to seek respite was noted as very difficult to initiate because it required the caregivers to look inward and admit some increased vulnerability.

Support groups were noted as being helpful for many families throughout the whole AD process. However, during the time of decision-making and placement, the major level of support was provided in two directions; first, in the caregiving role and second, for the caregiver as an individual. In the caregiving role, the group helped not only during the decision-making time but with insights and clues at the actual time of placement. Through the group's sharing of their experiences and feelings around making the decision, the actual placement, and some early adjustments, caregivers were provided with additional resources for coping with their own feelings. Although this support didn't make the decision to move and the move itself less painful, caregivers were aware that others, too, had walked in their shoes and survived. Details of these findings will be presented in a later section on the caregivers after the move.

Interestingly, the caregivers identified themselves as a third source of support in the difficult decisions they were making. They cited their gut feelings, their intuition and their common sense as major points of influence. Often deciding that they had "gone the limit", they perceived these abilities as a sense of empowerment. It was their right to do what they were doing and decide what they were deciding. A large hurdle in arriving at self support was dealing with the absence of validation of their caregiving efforts by the care receiver. By the time they were at this decision-point the AD process has robbed the care receiver of the ability to provide reciprocal feedback.

It is interesting to note that of the ten separate interviews, only two, one adult daughter and the other a female spouse, mentioned God or religion in their discussion. An adult son, shared an interesting philosophical perspective:

I mean (laugh) it's a human problem now and you can keep that out of it because no amount of faith is going to change this one hellish job.

In summary, the caregivers identified the key sources of support as formal, informal, and self. Overall, individuals in the health care system were perceived as a negative source of support and tend to prolong the decision to access formal care. Family members, home health, and respite services provided significant and positive support and reinforced their decision to continue in their caregiving at home. However, noticeable by its minimal reference in the discussions was the care receivers' ability to exert any active influence on either these support systems or the resulting decisions.

### **Options and Availability**

As caregivers realized they were closing in on the time of placement, their major focus Included:

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identifying the type of care that would be needed, becoming acquainted with individual facilities, and dealing with the availability of a desired site. They identified **pre-planning, beliefs and values, and realities** as the key issues influencing their decision.

**Pre-planning** was best described as making visits to several formal care facilities and then making a decision to place their care receivers name on a waiting list. On hindsight, many of the caregivers identified how they had flirted with the issues of pre-planning but had not taken any initiative to follow through. This was an extremely difficult process for the caregiver to undertake which they described very poignantly as, *trying to visit but resisting the move*.

The **beliefs and values** of the caregiving spouse and child are the key elements involved in the dichotomy between resisting and deciding to making the move. They described very basic family-personal values, as well as their own Individual philosophy. The myth of abandonment was clearly refuted. Caregivers noted, "you make commitments and follow through." "You go the limit." "Its a child's responsibility to their parent." "I am caregiving because I love my mother, not because I feel obligated."

Families arrive at the placement decision by considering the **realities**, which they labeled the practical issues. The absolute first reality is an open space in the facility at their care receiver's level of need. Three of the caregivers who were on waiting lists found the facility unavailable at their actual time of need. Two of these individuals found it necessary to seek another facility while the third caregiver found herself resorting to temporary facilities while waiting for the next opening at her original choice.

Well first, I had his name In at X (home 1), and then also at the X (home 2) and so when it became time, contacted them and they said they didn't have a place right then, but they would let me know when they would. (After a period of hospitalization-So the only place I could get him was at X (home 2) and so you know , that s about 20 miles or so from here, so I Just couldn't keep him there any longer than I needed to and so then I contacted the X (home 3) again and they said well they didn't have any place right then, but there was a man that was real sick so there could be an opening soon. So (husband) was out at X(home 2) for two weeks and then we got him in at X (home 3) where he's been ever since. And I'm real happy with the place. (Wife)

When she was in the hospital, we were making all these phone calls trying to find homes that would take her. They don't have any space even on an emergency basis to take a patient. (Daughter)

And so, then they'd give me names and you know by the time he was ready to come out, the place would be gone . . . (Wife)

A second reality, closeness in distance to the facility, emerged as a very important feature for both spouse and adult children. For the spouse it was mostly the need to assume increased driving demands, but for the adult child, It was now having to work another responsibility into their daily or weekly schedule.

Then it was zeroing in on a home in a proximity and the doctor and that's very difficult to do to zero in on one area really narrows it down. (Daughter)

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A lot of them in the neighborhood, right down here on (name of street) street, there's three of them. They own all of those .... I have a very heavy job. And I bring work home most of the time. (Wife)

What I liked about it is it's so close to home, that my dad could drive there to visit. Because he still gets confused driving. At that time, he was still getting confused. He just moved to X two years ago but he never quite got the road straight. And it's confusing out here. (Daughter)

Although families alluded to the financial impact of formal care decisions, at the practical level, their discussion was centered on identifying the *best* vs the *cheapest* for their care receiver. They became quite savvy at recognizing what the caregiving facility should offer to be the most appropriate place for their care receiver. New and 'outside attractive' didn't always mean the best. A male spouse shared:

There was one place, a very lovely place. "How about security?" "No, we're always right here." The nurse was back in this room, the clients were sitting out here to walk right off. A very high class-looking place. But there was no security at all. Silly, if anybody wandered away. (Husband)

One I thought was a good place, it was a new, modern home. They added an new section which was really, really nice and clean and everything there. But (sigh) then I soon found out that they overlooked my wife so much that she was just like a zombie, just like a zombie. (Husband)

As alluded to above, what kind of an impression the facility makes is factored into the decision. The caregivers described their debate here as between **facility features** and **human care**. **Facility features** incorporated the appearance, smells, sounds, levels of care, and organization. **Human care** was described simply and insightfully by a caregiver as the difference between sales people and individuals who demonstrate caring. As evidenced by these caregivers comments, a caring attitude on first impression, was quite influential.

.... but they just seem real human there. That's one of the reasons I picked that place. (Daughter)

.....finally found X (nursing home) and these people are just absolutely superior. I have never found my wife dirty. They are constantly around these patients. They are-they do an excellent job. I'm very happy for her. (Husband)

Finally, as families reviewed their options to finalize the placement decision, their beliefs and values, the amount of preparation they had invested and certainly the realities that presented themselves strongly influenced the actual formal care choice. Although these choices incorporated caregivers' best thinking at the time, they were quick to point out if the original option wasn't available and it was time to make the decision, they choose the next best option.

## Summary

As noted above, the journey to formal care took many different paths. The five themes explored

under the concept of reaching the end: making decisions, suggests how complicated and contingent this decision-making process was. The themes, presented in order of importance to the caregiver were: events, the health care system, caregiver-care receiver relationships, support, and options and availability. While the event could be a crisis, most often it was a turning point event that signaled the end. The one commonality caregivers experienced was exhaustion. The male caregiver was more likely to make a decision for placement as a result of a turning point event around an incontinence problem while the female spouse caregiver was triggered by an AD safety issue. The HCS most often was a negative influence and prolonged the placement decision. With the caregiver-care receiver relationship and support, the influences of past experiences were extremely powerful. Finally, even if the family had decided to place their care receiver on a waiting list, it was rare that an opening existed at the time of crisis or turning point. Any one of these factors can tip the decision either way and all of them can change almost overnight in ways that are unpredictable. Thus, by themselves they may not predict placement but in combination there was a profound effect leading to placement. However. It is worth noting, once the decision had been made and the transition to formal care had occurred, there was little likelihood of a return to caregiving at home.

## Chapter 3

### MAKING THE TRANSITION: PLACEMENT

The theme of this chapter is: what happens during the move to formal care? This is the time that's partly adjusting to not doing caregiving at home and partially getting used to the new environment as well as coping with the immediate consequences of the move. In this time of transition, both of these processes are going on at the same time.

The reader is reminded that the neutral zone is the second passage of the transition process. As noted by Bridges (1980), 'The neutral zone is not an important part of the transition process -- it is only

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a temporary state of loss to be endured'. The label 'neutral' should not be taken at face value. Although it is meant to reflect a 'time out' concept for the Individual, it is not reflective of what is going on inside. During this time the individual experiences confusion, feeling disconnected, isolated, lost, empty and emotionally unconnected to the present.

## **FINDINGS**

What is it like going between home and an established routine within formal care? This is deceptive because the care receiver is in one place or the other but the caregiver's mind is torn between the two, a very emotional and draining time. The caregivers describe this time period as anything but neutral as they shared their feelings and emotions.

The move to formal care is a time bounded shift. As the caregivers noted, something indeed has happened. Basically the shift results in three changes: 1) moving the care receiver to another setting, 2) relinquishment of some level of day-to-day care, and 3) confrontation of a new caregiving environment. The caregivers suddenly need to try to make sense of what is going on, especially in the immediate past in their home caregiving role. A great deal of reinterpretation results and they must now try to project a whole new future on this side of the transition. NOW is seen in a different light and NOW means something else. A real paradox happens at this time: the caregivers are 'trying to hold on while letting go.'

The pivotal piece in the development of the caregivers' transition to formal care is their recognition of the differences between caregiving at home and caregiving in the formal care facility. Immediately, family caregivers noted shifts in three major areas: **control**, **involvement**, and **personal reorganization**.

### **Control**

Overwhelmingly, the family caregivers sensed a change in control. They reflected, while at home, that the decisions and responsibility were solely in their hands, theirs alone. Now there are others who certainly dominate, if not control, the responsibility and decision-making. Female spouse caregivers often noted how this reaffirmed a previous loss of decision-making ability as the AD process had earlier robbed them of their couple shared decision-making. As several spouse and adult child caregivers noted, they were on new turf now and this also contributed to the issue of control. Finally, in seeking placement, caregivers had recognized the need for professional services and they anticipated, as this relationship evolved, control would be an early, if not constant issue. As an adult daughter shared:

Oh yes. And I certainly (sigh) you know, I'm trying to control what these doctors do .... I just really haven't agreed with what they were doing.

### **Involvement**

Discussion of changes in caregiving involvement brought an intensity to the interviews. Caregivers reflected changes first in purpose and then later in the actual caregiving activities. The major shift in purpose became one of changing their caregiving activities from total responsibility and care to one of monitoring. Monitoring served two functions, to maintain their relationship with the resident and

to provide an access for their newly self-delegated responsibility of evaluating the care by the formal care staff. Family members also saw their evaluation of staff as a way to deal with their loss of control issue. Initially, they perceived this staff evaluation would include the level of professional care staff was delivering and staff's ability to personalize care. Professional care evaluation included such areas as equipment, staff's AD knowledge, and the physical caregiving skill level of the staff. In exploring the initial concerns regarding the issue of personalization, caregivers quickly noted the staff's lack of personal knowledge of the resident, shared an awareness that there would be little things that could no longer be done for their resident and that, overall, there would be less flexibility in the daily schedule.

The first question caregivers asked themselves as they reflected on their continued role, was; do I want to continue to? If so, how? Their responses ranged from no desire to continue to desiring some degree of participation, often desiring to help with feedings. Caregivers operationalized their approach to caregiving participation via a visiting schedule. Visiting behaviors soon involved strategies and were a result of two sub issues, frequency and sharing. Some caregivers could only manage visiting once a week while others made a daily commitment. Spouses were more likely to take this on as a daily responsibility, choosing to do this by themselves. Adult children were more likely to share visiting with siblings and extended family as a two or three times a week activity.

### **Personal Reorganization**

Almost immediately, caregivers experienced a shift in personal reorganization. They had gone from total and constant physical care responsibility to having actual time for themselves. Although initially dealing with their physical and emotional exhaustion, they soon discovered a change not only from within themselves but in the environment at home. No longer a slave to a routine, most caregivers quickly felt a freedom to come and go. They remembered they could enjoy a life outside the day-to-day caregiving. Within this freedom to make other choices, they emphasized their option to continue to care for and love their resident. The changes, at home, ranged from feeling very lost and lonely to pure enjoyment of the quiet and relaxed atmosphere.

Regardless of the direction of their personal reorganization, caregivers stressed the accompanying intense feelings and emotions. As a son-in-law noted:

It just seems like when her mother went into that care facility, we were given our lives back.

The common caregiver phrases emerging with placement were, 'The moment has arrived' and 'It's time.' The key point stressed by these caregivers was emphasizing the actual transition to formal care, *doing it* vs the earlier *deciding*. However, the overwhelming message one received was the perception of the abrupt and traumatic end of their caregiving at home. Immediately, the caregivers identified the differences between caregiving at home and caregiving in formal care in the areas of control, involvement and personal reorganization. Shortly after placement the caregivers realized changes were also occurring in the relationship with their care receiver. The reader is reminded, that focus of this chapter is on the immediate consequences of placement. Long term issues that were faced by the caregiving family, the care receivers, and the formal care staff are discussed in detail in Chapter VI. It is important to note that with the placement in formal care, the care receiver will hereafter be referred to as the resident.

### **Consequences**

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Chapter 3: Placement

Immediately there were reactions and responses by caregivers to this change in the caregiving site. The caregiving role and relationship had been massively transformed and there were real consequences for the caregiver-resident relationship, the resident, and the caregiver based on this transition.

Within the caregiver-resident relationship, what kept their role as caregiver alive was the continued commitment to promoting, maintaining, and preserving the integrity of the resident. Although the AD process had robbed them of any reciprocity from the resident in this relationship, the importance of the resident to them remained the centrality of their caregiving role. This finding supports the earlier work of Bowers (1987) and her concept of protective care. Most stressful for the caregiver, within this context, was the resident's inability to recognize how hard they were working to remain involved in their resident's caregiving. Dialogue from three male spouse caregivers illustrate:

...well I can remember when she was in the nursing home, I'd take her hand, hold her hand, and held her hand an awful lot and give her a kiss and t says X would you like to give me a kiss? . . . it's a tough situation when you lose a person, that the mind is gone and that's the way it is with these people . . . I says, 'X,' I have to leave now, she showed absolutely no emotion at all about it.

...And like I said, I go for a walk with her or go out, but not that it makes any difference, my wife, I don't think she knows. She just simply doesn't. And very, very, very, very few times that maybe . . . all of a sudden her eyes went open and she came to her full senses 'Oh my man,' she said and was gone Just like that again. As soon as I squeezed her and hugged her and oh, that moment everything was gone again. She was right back in her own world again.

Well pretty much the same. I go out in the afternoon-Sunday afternoon. She's up, sitting in the chair, and she recognizes me in a way. I don't know she recognizes me. And we usually take a little walk. I'm there for an hour, an hour and a half, and I come home. She welcomes me in a sense when I come, she doesn't really miss me when I leave. She acts like I'm just going around the corner and I'll be back in a few minutes anyway.

The consequences of the move to formal care for the resident are often difficult to detect and decipher. First, the caregiver was in the best position to evaluate the effects of the transition, having the past history and baseline for the most recent resident behaviors. However, the caregiver was in a time of great personal stress and may not have been the most reliable Judge at this time. Secondly, any decline in the resident could result from the progression of the AD process, be it a response to the change in the caregiving environment, a change in the physical caregiver, or from all three. Caregivers cited behavior changes and physical changes. Whether pacing, swearing, zombie-like, or aggressive behaviors were described, all were recalled as changes since admission and represented extreme trauma for the family caregivers. It would, however, be impossible, and impractical, to isolate the cause and effect. Finally, as noted earlier, there was the lack of reciprocity from the resident. The caregiver was unable to rely on the verbal feedback or the mood of the resident as a barometer to the quality of care being given by these new caregiving individuals, the staff.

The caregivers were able to identify four personal consequences in this early time of transition. They described **feelings, responsibilities for self, other residents, and role shifts**. Their discussion was usually direct and to the point, yet they shared the intensity of feeling and emotion that accompanied this experience.

**a. Feelings.** Almost immediately, caregivers noted an intense roller coaster type effect. They had

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experienced the ups and downs of caregiving in the past but these current feelings were intense. Most often their first mention was of guilt, as these interview excerpts reveal.

So my main reason was lack of sleep, that was -- otherwise I would have taken care of my wife much longer because I still feel so goddamn guilty about this whole thing, you wouldn't believe it. I feel so guilty that I put her in a nursing home, that many times I can sleep because I always think God, what does my wife think of me .... this tremendous pressure is gone, but on the other hand, the guilt feeling has not left me yet. I still have a guilty feeling I let my wife down for some reason or the other -- that is still there, even after two years . . . my brain tells me I did the right thing; and heart tells me hey, couldn't you have done a little bit more? Couldn't you have done, Just maybe you could have done this? (Husband)

So putting her out of my life was a very difficult thing. I hungered too long but since X care center is close to the house, I think we can still be a part of it, but It's difficult. It's even difficult to go down there because the guilt still comes in, but I did ah, still wish I could have kept her at home. (Son)

Then there's the guilt too -- part of it is guilt like I really should be coming more often but I know I can't and I don't have to, but, I should but, she doesn't know the difference but, I still should you know. So you have this stuff going on and the pressure builds up if you don't get there. (Daughter)

However, the best example of the ambivalence and intensity of these feelings was summed up in this quote by an adult son, 'In the guilt, I feel relief'. This son had noted, early in the interview, his intense feelings toward the placement decision. However, since he had made it past that hurdle he now thought her death would be the ultimate loss.

I don't know if It will be a relief for us or it will be a horrendous challenge. I'm frightened of her death in a way. When I first put her in, I thought well, she'll be well taken care of, I can still be part of this process and all, and there's a great relief within the guilt, but I don't know. I sometimes think her death will probably be worse now than if she died right here at home, which would have been preferable. Because that's what I was holding out for was I was thinking she would die here where I thought the most noble kind of death and dignified death would be here at home.

**b. Responsibility for self.** When the caregivers turned to sharing a realization of their need to assume some responsibility for themselves, they spoke most often of time and new stressors. Adult children now needed to find a way to work in visiting during an already hectic schedule. Spouses, however, often found themselves either with time on their hands or filled the days by spending most of it at the nursing home. Mostly the stress referred to dealing with their physical and emotional exhaustion, the suddenness in the caregiving site change, and the felt need to recognize and respond to the caregiving role changes. However, there was at least one spouse caregiver who noted the stress brought on by the void left in his life at home.

I go out once a week. I can hardly stand that. And so leaving; not getting, not being with her, but leaving. Just like turning the blade on the lawn, you know . . . You know, I have everything -- all the other activities, but I don't have to take care of her which gives me time which lets me look out the window when I should be doing something . . . I Just don't have the drive to

use it (freedom) half the time now. But I waste it, unfortunately . . . I don't have nobody to talk to. (Husband)

**c. Other resident.** A clear majority of the caregivers were unprepared for the feelings they would experience when they were confronted with a ward or unit of AD residents. Some found the behaviors engulfing, as everywhere they looked they saw the variety, intensity and complexity of Alzheimer's symptoms. Others were saddened to realize the behaviors they observed represented the future symptoms their resident might exhibit. Often, as described, it was an overwhelming beginning experience.

**d. Role shift.** The role shift brought a recognition and redefinition of the caregiving responsibilities. As caregivers shared earlier, their first Job was to recognize the differences from caregiving at home. Initially, the caregiver's emphasis was on recognition of their perceived new responsibilities. After they had a period of time to interact with the staff, their focus shifted to the development of new strategies which allowed them to remain involved in the formal caregiving role.

In summary, the care receiver became a resident in formal care. However, for the caregivers, they found themselves torn between dealing with the loss of caregiving at home while trying to respond to issues in the new caregiving site. The caregivers early on recognized two important themes within this transition: first, how caregiving in formal care differed from caregiving at home and second, what were the consequences of this move to formal care. The caregivers identified differences between home and formal care in the areas of control, involvement, and personal reorganization. Although aware of consequences for the resident and their resident-caregiver relationship, caregivers focused mostly on their personal consequences of feelings, role shifts, other residents, and responsibilities for self. As we listen to the caregivers one recognizes they have made the transition to formal care. With this transition came new responsibilities, especially the need to deal with formal care staff. The development of these relationships between family caregivers and formal care staff is the central topic of the next section.

## Chapter 4

### THE MOVE BEYOND

The purpose of this chapter is to explore the caregivers' adaptation to a new way of life. These individuals described themselves as in the process of developing a relationship with the staff who now are, in essence, the primary caregivers.

Bridges (1980) called this third passage in the transition process, 'New Beginnings.' In this phase the individual launches into a new activity. As Bridges shares, 'New beginnings are accessible to everyone and everyone has trouble with them'. The outcome from this time period depends on an internal or inner realignment rather than external changes. It's during this time that the individual

struggles with letting go of the old way of doing things. As the individual emerges from this experience he/she may be described as changed, renewed or refocused.

In acknowledging the caregiver's complete transition to formal care it is critical that one considers the longer term transformations. The concept of the move beyond incorporates a recognition that relationships take time to develop and that the families' caregiving role transition evolves through perception and evaluation of shared experiences with staff. In this over-time process in formal care, family caregivers identified three major themes: caregiver-staff relationships, factors influencing the nature of the formal caregiving relationship and caregiver evaluation of quality of care. Although some of the sub-areas will not be new issues, they have by now taken on increased intensity and meaning.

## CAREGIVER-STAFF RELATIONSHIP

The big theme and what really matters most to the family caregivers is the relationship with the formal care staff. As explored earlier, relationship development involves time, energy and commitment from the family caregivers. However, adding to the complexity in this situation, caregivers identified a two-step process they negotiated. First, is a **recognition of the change in their caregiving role**. Second, is the **establishment of a relationship with the formal care staff**.

The caregivers' roles and relationships have been greatly transformed and there are also real consequences for the caregiver-care receiver relationship based on this transition. In this new relationship, recognition and redefinition of the new caregiving responsibilities must occur. What keeps their role as caregiver alive is their continued commitment to promoting, maintaining and preserving the integrity of the care receiver. Thus, as they begin in the formal caregiving process, the caregiver's focus is on promotion and construction of the role rather than the caregiver-care receiver relationship.

It is obvious that over time, the resident will continue to decline. Now, the caregivers finds themselves needing to decide if this is a result of the disease process, or a change in environment and staff. The caregivers are challenged because not only do they have a lack of resident reciprocity, they also have no validation of poor staff care If they perceive this is the situation.

Reflecting on their continued involvement In formal care, caregivers discovered a need to *refocus*. As they recognized their responsibilities in this changed caregiving role, it was extremely clear a new relationship had been forged. When caregiving at home, there was a relationship between the caregiver and the care receiver. Since the transition to formal care, the caregiving relationship has been modified to include the addition of staff. It has now become a critical responsibility of the caregivers to assess the staff as well as their resident.

This caregiver relationship with the staff takes time to plan and carry out. Maybe this is why even though formal caregiving may not be as physically draining as home caregiving, it continues to be as emotionally draining. Comments from an adult son caregiver provide an example:

There are a few of them, a few people over a period of time who have made me feel really good about coming in, but whether it's my nature or what, I feel sometimes that I'm the one that has to break the ice, provide the humor to make everyone feel good.

## Aides

Although staff relationship was the central theme in exploring the move to formal care, the details of the discussions centered on the caregivers perceptions of and relationships with the aides.

Table I shows a breakdown of how in the focus group discussions, family caregivers' 142 mentions

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of formal care staff were divided between positive and negative references to different categories of staff. Two themes are particularly notable in these data. First, over half of all the mentions involved nurses aides. Second, the mentions of aides were much more positive than any of the other groups. Indeed, the 25 percent negative rate for mentions of aides may be an overestimate, as over half of these mentions involved problems that were due to aides carrying out institutional policies and procedures.

The major reason for this emphasis on aides was that aides were the ones that family members consistently found providing the direct care to their family member. One spouse shared, "Only the aides take care of the patient. The nurse doesn't do a thing but administer medicine, that's all." An important reason why family members discussed aides so positively was an identification issue. It was the aides who now substituted for the tasks that family members used to do. In addition the aides were the ones who really knew their family members' needs in technical and personal terms. These points were nicely illustrated in an individual interview with an adult son:

TABLE I

POSITIVE AND NEGATIVE MENTIONS OF FORMAL CARE STAFF  
BY FAMILY CAREGIVERS IN GROUP INTERVIEWS

	<u>Nursing Administrative Facility</u>			
	<u>Staff</u>	<u>Staff</u>	<u>Staff</u>	<u>In General</u>
Positive Statements	75.3%	36.7%	28.6%	38.1%
Negative Statements	24.7%	63.3%	71.4%	61.9%
(Frequency)	(77)	(30)	(14)	(21)

Now rarely do you get personalized observations out of a nurse . . . it's the aides . . . and I sometimes think why aren't the nurses more this way? But the aides do the hard work and you see the difference and you have so much respect for them because this is the person you care about and this is the person who is dressing them, undressing them, taking them to the bathroom, feeding them, bathing them. The most intimate things are being done by these people.

In particular, other than occasional mentions of frustration with nurses' low level of direct involvement and doctor's almost complete absence from the setting, discussions of interactions with staff was predominantly about interactions with aides. This combination of consistent contact with aides and a shared understanding of the kind of caregiving the aides do lead family members to emphasize their contact with aides and to talk about these contacts in a highly positive manner. Thus, in the family members' discussions about what staff were involved in providing care in nursing homes, it was the aides who played the central role. While it is important to know who the major staff players are, it is also critical to explore what it is in this new relationship that makes it work and what hinders its best function.

In summary, development of the relationship with the formal care staff was identified by family as the most important adjustment in their transition to the formal caregiving role. Perceiving a need

to refocus, the family caregivers recognize the caregiver-care receiver relationship was modified to incorporate the formal care staff. The aide was the staff member family most consistently and positively identified. This perception results from not only a personal identification with the aides caregiving but also they are the ones the family member constantly finds taking direct care of their resident.

#### FACTORS INFLUENCING THE NATURE OF THE FORMAL CAREGIVING RELATIONSHIP

The second theme family members identified in their adjustment to formal care explored the factors that influence the nature of the formal caregiving relationship. Caregivers' bring all their previous health care system experiences with them. As noted in the earlier pre-place-merit discussions of health care organizations, these perceptions and experiences had been good or bad, no in-between. The important factors caregivers' identified that affect the nature of the formal caregiving relationship included: monitoring, trust, staff behaviors and family behaviors.

#### **Monitoring**

The caregivers monitoring behaviors become a key strategy in the overall development of the caregiver-staff relationship. Monitoring also becomes the crucial link in the development of trust. However, it is also a critical behavior which provides caregivers the opportunities to make observations, form perceptions and provide reciprocity to staff.

Caregivers were very open in sharing their monitoring goal. Simply put, they monitor to 'keep good homes good.' They know staff are aware of which families stay involved with their residents. Early on, they themselves became aware of those residents who had no visitors. However, to monitor was not just to show up; it involved developing strategies. Much energy was put into timing visits and observing staff interaction with other residents. Caregivers pointed out it was important to vary not only the days but the time of day they visited. They became sophisticated enough to be able to evaluate the difference between daily shift staffing and weekend staffing.

I just have a hell of a nice relationship with these people. I have a lot of confidence in them. Now with the swing shift, I'm not so sure. I'm -- I don't know. I don't uh, I was in there several times in the evenings and I don't think it is quite as efficient as it is on the day shift, but no complaints. (Husband)

They're understaffed. A lot of times I go on weekends, and they don't show up, they don't go to work. That means they're short handed. (Wife)

There was no secret to how these family perceptions were made. Family caregivers not only observe staff interactions and behaviors with their family member but they monitor staff's treatment of other patients as a barometer for how their family member will be treated when they are not present. This was also a consistent theme in the interviews.

But I think they treat other patients pretty well, I think. You're right, that gives you an indication of how they are to my mother when I'm not there. There's this one older fellow that's just demanding constantly and kind of like a broken record, 'Nurse, nurse, give me my, I want my, nurse, nurse.' I mean it goes on 24 hours a day. But they never really lose patience with him and they don't ignore him either so that makes me feel good. (Daughter)

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And they handle other situations like last Sunday in the day room, they gave a lady a glass of milk which she managed to drop on the floor. I was leaving the dayroom but I was so curious as to what they would do. No problem. Nice. (Spouse)

Oh yea, because you know, during the time that you're in there, you notice if they were gently treated and with lots of patients, there wasn't any yelling at anybody. (Husband)

Thus, through observation of staff with other residents, particularly those who appeared without family, the caregivers developed a sense of what was happening when their resident needed help and they were not there. As noted earlier, this monitoring strategy was a key link in the development of trust.

### **Trust**

A first on the road to the formal caregiving relationship is the development of trust. Without an ability to trust, there is no chance for a positive caregiver-staff relationship to develop. Caregivers were quick to note the importance of including both the facility and the staff within their level of trust. Repeated interactions, again over time, are the cornerstone for the development of trust. Most often the validating experience was finding that a requested caregiving behavior had been carried out by the staff.

Yeah, they do and they're very good about you know, when he was up and around, they'll say -- they would call me and say 'We found X on the floor, he had fallen or whatever, and we wanted you to know that he did and that he seems to be okay and everything. (Wife)

The nurses would call me if there was any change. He would even fall out of his chair, go to sleep and fall out of the chair right in front of the nurses desk and they would call me and tell me, He took a tumble out of his chair but he, she said we checked him very carefully and he's alright. If I didn't happen to be there or they would call me at night if he was more disturbed than usual and let me know. (Wife)

But they always contacted me. It didn't seem to be any problem. I'd say, 'Okay, fine. Thank you.' And that was about it. (Husband)

...I was making suggestions like I thought I'd like to hang a mobile over her bed because I said, 'She lies on her back in bed so much.' 'Great idea, we'll have a hook put up above her bed, and you can bring that in.' And I did .... And I said 'Do you think you could walk her?' 'Oh we're trying to walk her, you know,' so they were receptive to my ideas and like we were going to be a team even though I'm not there. (Daughter)

Thus, when monitoring shows desirable staff behaviors, the result is a positive outcome, the development of trust. What this commentary is also conveying is that family caregivers are making observations and forming perceptions of staff behaviors.

### **Staff Behaviors**

Within the exploration of the formal caregiving relationship and the dynamics of their interaction

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with staff, caregivers devoted considerable attention to the influence of staff behaviors. Just as family caregivers were clear about who was doing the care, they also knew what they wanted them to be doing.

Two categories of behaviors were particularly prominent in the caregivers' viewpoint. While some discussion focused on behaviors that reflected the *staff's relationship with the resident*, their major emphasis was given to behaviors indicative of the *staff's relationship with them as caregivers*.

It's notable that the family's priority in the staff-resident relationship was similar to what Bowers (1988) found under her heading of preserving the identity of the resident, treating the resident as a person rather than an object of care. What this amounted to was family caregiver's thinking of quality care as involving an inseparable combination of technical quality and respect for the resident. As evidence of high quality care, family caregivers wanted to see the staff develop a personal and/or professionally sensitive relationship with the resident.

Especially here, the gals in that special care unit, they do know. That's why Mom has adjusted there. They don't force her to do anything. If she doesn't want to do it, she doesn't do it. They just leave her alone, and come back five minutes later as if they've never mentioned it and say, "Let's do this." and she'll do it. Before, in the other places, you either get dressed now or ] don't have time to come back, and you do this now and they make an issue out of it, and so you have an upset patient. (Daughter)

A dialogue about the aides:

A: They're so tolerant. That the only thing that makes all this workable. (Daughter)

B: And they also touch and that's so important. And brush with the hand, pat on the hand.  
(Daughter)

C: Or hug. (Wife)

D: And a very positive attitude. (Son-in-law)

B: That would be hard to be a caregiver daily. I just thank God for these people... (Daughter)

During an interview, an adult son shared:

Well, I don't know what their commitment is to life and what their background is -- whether it's a religious background or they just have all this compassion for people. And one of them gets sick with back problems and another one is off sick at times and you see the place really changing. So certain people have just kind of a unique quality.

Turning to staff-caregiver relationships, these emerged as not only a personal but a sensitive and priority area for their discussion. Family members were quick to point out that it takes both family and staff working together to develop a relationship. A daughter shared in her interview:

It's funny, they're individuals of course. Some of them are just ever so kind and helpful and communicative and some of them are just put offish completely. They just -- it's like you're invading their territory or something you know, 'and we sure hope you leave pretty soon so we can get back to business.' Others of them make you feel like you could be their best friend. And you're both in this together and they just want to do what's the best thing for your mother. (Daughter)

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Another daughter shared this staff response at the time of her mother's death:

She made it clear to everyone that if she was to die, she wanted someone to put her eyebrows on . . . she stayed up with her in the next room, and that night when she died, she got up and she put her eyebrows on before she called us. And when we got there was a rosebud on her bed.

Other caregivers shared:

If they had understanding for the family. That's the biggest thing. (Daughter)

I felt that they were concerned about me as well as him. (Wife)

You see, one of the little aides put her arm around my shoulder--a little Cambodian girl who I think is just great. (Husband)

The caregiving relationship is enhanced when staff recognize the caregivers by name and when they share about the resident's activities, appearances and behaviors. A particularly powerful sharing can occur when staff validate caregivers' past experiences. As staff and caregivers discussed caregiving experiences, caregivers could receive reassurances that many of the problems they experienced were encountered by the staff as well.

We had always had a good relationship, and I was disturbed when I had her at home that it was completely deteriorated to, you know, having her be angry at me all the time. But I know some of these people who take care of her at the home said that she can get angry at them sometimes I think that it surprises some of them out there because they think she looks like such a sweet little old lady, but she can be a little witch. (Daughter)

Well, I find that it's much easier to be one of the good guys now instead of one of the bad guys! (Laughter) She gives them so much problem that I know she used to get angry at me, and now I'm the one that she can smile at. I can enjoy it more, and she can enjoy me. (Daughter)

Although family caregivers realized their new team role is likely to be secondary to that of staff, they often were very knowledgeable about the disease process in general and certainly their resident in particular. They were aware of the past history with medications or aspects of the environment such as noise level or patient's personal reactions such as being overstimulated by TV or rock music, now being played by staff. Thus, the caregiver had a baseline for observing the resident's response to institutionalization and often their evaluation influenced whether the resident stayed or moved to another facility. After all, family members seek formal care to get better care. The team relationship is facilitated if staff view the family's behavior in this process as interest in the resident rather than a desire to harass or threaten staff.

Here, anytime I have said anything to them that might help, they say, 'Thanks for telling me that. We'll try that..... I think that's another reason why I've appreciated this place is that they do take a suggestion as if they're interested to hear them. (Daughter)

## Family Behaviors

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As noted above, family caregivers recognized they bring not only desires but responsibilities to this developing relationship. Caregivers often shared how they felt a need to actively influence the relationship with staff. Here too, they initiated purposeful strategies.

We've come to the conclusion now that the purpose of the visit is to show the staff that you care. (Daughter)

As a common strategy, they provided care to their family member in ways that they hoped would provide *role modeling* for the staff. Since role modeling implies a presence with the resident, the interrelationships between strategies of monitoring, visiting, role modeling and trust begins to be obvious. Family caregivers were also aware of the importance of communication, thus they intentionally gave positive feedback to staff as a way of influencing staff to provide higher quality of care for their family member. All of the above activities were ways in which the caregivers actively participated in not only observing but molding staff's behavior to create the best quality of care for their patient.

And I did not get through to anybody that this wasn't just a stick lying here that they were treating until I got this little nurse and I was asking her questions, and she said, "She can't hear." So I said, "How old is your grandmother?" And the nurse looked at me, "Oh, well, she's -- whatever --" I said, "She's like your grandmother," and then she started treating her like a person. (Daughter-in-law)

Thus, role modeling was a common strategy used by caregivers to help promote the family caregiver-staff relationship. Family members expect sensitive and professional behaviors toward not only the resident but themselves as well. They share a willingness to reciprocate in a staff relationship that is already positive and a desire to make contributions to improve those that need help. In summary, family members identified monitoring, trust, staff behaviors and family behaviors as the important factors that influence the nature of the formal caregiving relationship. Monitoring as a strategy is a key link in the development of trust. Trust is critical to the development of the caregiver-staff relationship. While family expect staff behaviors that provide for a sensitive relationship with the resident, their major focus was on the staff behaviors that influence a supportive relationship with themselves as caregivers. Recognizing they have responsibilities, family members often use role modeling to help promote the family caregiver-staff relationship.

### FAMILY CAREGIVER EVALUATION OF QUALITY OF CARE

The final theme in the adjustment to formal care centered on the caregivers' exploration of the quality of care issue. Family caregivers spoke with one voice on this issue, they expect quality of care. When they were the single caregivers at home, they provided the resident with loving and competent care. Now, with a team of caregivers, there is no excuse for anything less.

How do family caregivers go about evaluating for quality of care? To be clear about what is desired in a relationship is one piece of the puzzle. However, it is often difficult to know how to evaluate the factors involved in the actual caregiving. Family caregivers identified three areas that they included in their evaluation: the quality of care for their resident, staff knowledge, and the organization of the formal care facility. Quality of care, they were quick to point out, equated to *respect for their resident*.

## Quality of Care

In the family caregiver's evaluation of care, there was very little identification, let alone discussion of caregiving tasks. When specific tasks did come up, the caregivers discussed activities such as dressing and toileting in ways that were most meaningful to them. For example, dressing involved providing their resident with clothes that matched and were not soiled, and toileting needed to be accomplished in a way that protected modesty and privacy. Just as Bowers (1987, 1988) discovered, family caregivers are more likely to relate their caregiving experiences in terms of the meaning that experiences have for them rather than the specific tasks that come with their caregiving activities.

Family caregivers identified their emotional involvement, love, and personal motivation that provided the basis for their care at home and that they continued to bring to the formal setting. As explored in his text, *On Caring*, Mayeroff (1971) relates this caring process involves time and patience. The caregiver's vision of caring was not a passive result but one in which they were an active participant. At this time, in the adjustment to formal caregiving the vision of caring continues, as on a continuum. Changes in their role and the resident occur and will continue to do so, just as it did while caregiving at home. A key concept within the caring process is the idea of not only being with someone but also being for them as well. '... in caring for another person we can be said to be basically with him in his world, in contrast to simply knowing about him from outside' (Mayeroff, 1971, p. 32). Thus, quality of care for these family caregivers is influenced from at least two perspectives. First, as a continuation of their past shared caregiver-care receiver commitment. Second, in response to their personal relationship loss within the AD process, they will struggle to be for their resident and not just with them.

Staff must do their care in a heavily restrictive organizational setting. Quality of care for a nursing home makes smooth functioning of the organization a high priority. This was often at odds with the fact that staff must do their care in a heavily restrictive organizational setting. Quality of care for a nursing home makes smooth functioning of the organization a high priority, while for family members it means emotional, bonded care between caregivers and residents. The difference in these two perspectives leaves a lot of room for misunderstanding. Aides are often caught in the middle, as they are the employees in the organization who not only provide the majority of the direct care for the resident, but also have the most contact with the family.

Family comments are captured in the following dialogue:

A: Most of the aides I've met are really good, and it makes me so mad. The facility will say, 'Oh, we'll hire if we can just get them.' and they don't. That's just a bunch of bull. (Daughter)

B: They've got good ones down there. You know, the ones that stay, they're alright, but they have some who came in extra . . . would just lay around and wouldn't -- there's something to do all the time in a nursing home in order to keep it -- and you've just got to keep ahead of your work. (Husband)

A: But you know, one I talked with where my mother is, she's really a good little gal. She's been a nurse's aide for about ten years, and she said if she complained really, they would just tell her to leave. If she left that facility, she would have to start at minimum at another one . . . They are not appreciated. Makes me mad! And if you complain, like if my mother, if I think something's not fair that's happening to her, if I complain, it would be the aides that get

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hell, and that isn't the point. It's because there aren't enough of them. (Daughter)

In an interview an adult son disclosed:

And know that when you go there, that one person you enjoyed so much as the caregiver may be gone tomorrow and you're constantly going to be retraining yourself to that new person that comes on and you're going to be fatigued by it because you're thinking, 'Oh God, now I've got to deal with this one.' and you look at all the problems you're going to have there. Well, so you deal with it. You don't have a fixed situation. It's always in transition. The turnover rate is horrendous.

You look at the staff here, there's an incredible turnover. Why? They're overworked and underpaid. That's simple. This is an incredibly labor intensive business, particularly when you're talking Alzheimer's. (Husband)

Thus, caregivers who identified the quality of care they desired for their resident often found themselves in a system that had a different definition. While they expected quality from all staff, an aide who was skilled and knowledgeable was often a key link to the caregivers positive perception of care.

### **Knowledge base**

Family caregivers bring a great deal of knowledge about AD and their resident as an Individual with this disease to the placement. They have been in interaction with health team members, support groups, and formal organizations. Also, they often seek printed resources and access professionals, such as lawyers, on their own. When family caregivers began to interpret and evaluate staff members, they identified with the physical or "bed and body" work of the aides because that is what they used to do. While they expected all staff to have a knowledge base about dementia, it was crucial that staff also be trained in appropriate professional behaviors.

There just wasn't the knowledge then. Now when there is the knowledge out there and it can be obtained, now I do blame them. I do blame aides in nursing homes that don't understand various forms of dementia. I do blame the hospital workers who don't understand and react the wrong way. (Wife)

As family caregivers seek a quality of care for their resident, they are not only evaluating individuals but the facility. Thus, the setting and its guidelines exert a controlling influence overall.

### **Organization of the formal care facility**

There were a number of things that affected caregivers' perception of the quality of care but an underlying theme that kept coming up repeatedly was the organizational setting and the ways the organizational setting influenced the staffs' ability to deliver care. This was particularly important in the staff's ability to deliver care in ways that made the caregiver feel there was a high quality of care delivered in that facility.

Earlier the discussion acknowledged the caregiver-staff relationship that develops over time. The emphasis the caregiver places on the aides was also explored. However, caregivers also recognized

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the demands of staff caregiving in a heavily restrictive organizational setting. There is too much work to be done within their quality of care guidelines, and there is too little pay to reward a staff member for that level of care. Staff who attempt this level of care may not only go unrecognized, but it may even cause problems for themselves within this system. However, family caregivers sense that this quality of care is how they provided care at home and upon turning to formal care this is how they expect the system to provide care for their resident. This is why we see the caregivers involved, to provide for the quality dimension and their desire to get as much out of the staff as they can.

In an attempt to look more closely at the organization of the nursing home and the caregiving role it is useful to recall our earlier discussion of caregiving tasks. Linking technical tasks with the formal organization and non-technical tasks with the family suggest that nursing homes and the caregiving families are currently in a state of imbalance. It is assumed that while the goals of both groups are complementary, their structures are in conflict and herein lies the basic problem. When routinization is a major focus, the description sounds more like a machine or an assembly line product rather than a process that incorporates human beings that have the ability to be caring, sensitive and respectful. However, to support an optimal family-staff relationship, the interaction processes between family and staff could assume as much importance in accomplishing the task as the actual task consolation.

Thus, at an optimal organizational level, staff caregiving delivered in a caring way could be valued by both the family and the formal organization without having to incur additional expense. Basically, this is a process-relationship issue and not a focus on the actual task. In the long run, this approach is also responsive to the issue of family as the 'forgotten clients.'

While there was an attempt above, to discuss both quality care and organizations separately, the exploration of quality care within a formal care organization is considerably more realistic and practical. At the same time as caregivers see staffs' work being invalidated in the nursing home and they see no respect for adding that caring or respect dimension that they really want, they recognize quite fully that to the extent that the aides add a caring dimension, it detracts from the ability to meet the technical demands of the rest of the facility. Still, as far as caregivers are concerned, that is what quality of care consists of. Thus, they end up seeing that the person doing the job that they most empathize with is when they are most aware that the demands of the system and the rewards of the system are completely out of line with what they see that person is doing. The caregivers seem to be saying, that these staff are as unrecognized and stressed in their caregiver roles in this system as I was unrecognized and stressed in my caregiver role at home when I was the only one.

Over all, on a broad level, families still want to see some clear sign of respect for the resident. Their care comes out of years of commitment and obligations and technically excellent care is not a substitute for the bonded family care they gave at home.

With the focus on working together as important as preoccupation with tasks and structure, the formal organization and the family could identify their contributions to a mutually identified optimal caregiving outcome. Competence is certainly necessary from the family's point of view, but mere competence is not enough. The bottom line would be not only *what* these two groups do but *how* it is done.

Thus what really matters from the family's point of view and the involvement of the family in formal caregiving organizations is centered within the organizational structure. As caregivers make the move toward this new beginning, issues of where they fit, how the formal care facility is organized, how they comprehend or fail to comprehend important agendas, and how they find a place in or fail to find a place within that organizational structure are crucial.

In summary, in exploring their formal caregiving experiences, family caregivers do make a new beginning. They are able, over time, to refocus their caregiving relationship with their resident to

incorporate the staff. They plan strategies, such as visiting, role modeling and monitoring. It is through these techniques that they arrive at the ability to develop trust.

In their discussions, family caregivers most often reflected on their relationship with the staff, identified factors that affect the nature of this relationship, and shared insights into how they evaluated this new caregiving relationship. The aides are the central staff individual for family members. Family caregivers expect a quality of care for their resident even though they all must function within a restrictive, formal care organization. This quality of care, however, involved a recognition of themselves as caregivers as well as a recognition of their resident as an individual. As noted earlier, the challenge for the staff and the formal care organization is to also *care about* the residents rather than only *take competent care* of them.

## Chapter 5

### DISCUSSION

The past three chapters have moved with family caregivers and their AD residents through the decisions that ended their caregiving at home, into the formal care placement and left them as they were developing their relationship with formal care staff. One of the things that Chapter I highlighted as an issue underlying all of the various phases of the transition would be potential issues in **spouse-adult child** differences. Beyond that, other areas that showed a consistent relevance were **family** and **surviving**. Within family, the important dyad of **caregiver-care receiver relationship** will be shown to play an integral role in better understanding family caregivers' experiences around the transition to formal care. The overall discussion will move from family, which is at a social, interactive and support level to surviving, which is at the individual level. An important and relevant reminder: The choice

of a qualitative approach provides a window through which one can peer into the individual world of the caregivers. Thus, the type of caregiver provides a first clue to differences in caregiving issues.

### **SPOUSE-ADULT CHILD**

A key objective of each research question and one theme that has been looked at explicitly but separately within each of the sections is the difference between spouse caregivers and adult child caregivers. The first point of discussion is to look at the broader issues of that comparison not just at a specific point and time, since overall there are some systematic similarities and differences.

Both spouse and adult child caregivers experienced tremendous exhaustion with their caregiving experience. However, their reasons for placement seem to differ. Spouses, who tend to push themselves to the very end, find themselves most vulnerable to a physical crisis or an AD turning point event, such as safety for the females and incontinence for the males. Adult children are more likely to be vulnerable to an AD behavioral change or caregiving issue, like the need for respite or home health help. In the spouse relationship there is more equity and one continues with the caregiving stresses and AD changes, because the central hub of their life revolves around this relationship. With the adult child who is exhausted, trying to work and continue with family responsibilities, the changes in the parent causes a much different stress, in that while a significant responsibility, it is not their only one and may not even be the central one. In the parent-child relationship, most often the holding on as long as possible has to do with a reversal in the dependent-independent relationship. It is hard to recognize your parent as the dependent one, as these caregivers share:

So putting her out of my life was a very difficult thing.... but inside you can feel that feeling of abandonment. I abandoned her and I didn't want to. As I say, I wish she could have died.  
(Son)

.... I felt like no one else was going to look after them. By God, somebody's got to look after them. (Daughter)

There is a difference in how spouses and adult children behave around the placement decision. Spouse often assumed the responsibility for making the placement decision and then just informed their kids and extended family. This is not to say that spouses don't discuss more general activities, but they perceive their offspring are too busy to be intimately involved. While these spouses most often spoke of positive relationships with their children, they identified limited involvement in the actual caregiving itself. However, this limited level of involvement was most often initiated by the spouse caregiver as they labeled their kids as families who were involved in parenting young children, both parents working or a single mother supporting the grandchildren. While some of the caregiving spouse's behaviors may come from their exhaustion level, or a desperate desire not to have to relive the many experiences by retelling them, the more common response was they don't want to burden or bother these already too busy adult children with other responsibilities. These behaviors also represented the spouse's attempt to remain an independent caregiver and not show dependency needs to their children. Examples from a male spouse care-giver and a female spouse caregiver provide some insight:

It was my decision but however, two of -- I called and talked with -- I have two sons anyway .... they were involved but not in the decision. I'm, I just said, told them beforehand, I said,

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"Well, the time will come I probably have to place mom in a nursing home.' And their response was, "Dad , you did all you can and that was that. (Husband)

Well, they realized that I couldn't handle it anymore and that I needed to get away from it and they of course are busy with their families and everything and they couldn't really give me too much support and you know, taking care of him or anything like that. So they, you know, well especially when he started becoming combative and everything. They thought that was the thing I should do. (Wife)

Adult children turn to their siblings or the remaining parent with more of a discussion-type decision. This process is not to imply that the decision comes easy or is unanimous. These behaviors are strongly tied up in the dependency-independency role shifts that placement will bring but may also of necessity be influenced by wishes of the other parent, siblings, and extended family. In contrast to the caregiving spouse who, in the past, has shared decisions one-on-one with the spouse, the adult child has no history or experience of being in a position of decision-making for a parent. For the adult children, it is as if they've lost the relationship with the parents but find themselves with the responsibility. This interesting dialogue is between an adult daughter and her husband:

Well, the only thing is that it's Just a body of the person that you have grown up with and through the years. It is no longer that person. (Son-in-law)

No, that's the memory that stays with you. (Daughter)

I know, but that's what it becomes. I mean, all the sudden out of a clear blue sky, that person that you knew is no longer there and it's Just that their body is there and it's a whole different personality. (Son-in-law)

Well, they are worse than a child, worse than anything. (Daughter and on-in-law)

With both the AD process and placement, spouses shared a great sense of loss. This seemed to be the case with both a short-term relationship of married just 3 years ago, as well as a long-term one going on 49 years together. There was (his huge void in their days and evenings, in their heart and their life in general. The caregivers had often become so involved with the caregiving, it had become their whole existence. The spouse misses not only the intimacy and relationship with their spouse but after placement often find themselves physically alone too.

Well, it's very lonely .... Just something you've got to keep doing. You know, you've got to hang in there and of course, my bad times are at night .... We were always real close and everything. (Wife)

. . . the car went bad and everything went wrong. I just wanted some comfort from X. I wanted him to say it was gonna be alright. He simply isn't there. We used to think we knew what we were going to do, that we'd be here. Sure, one of us would go, but we would be here together. (Wife)

Yeah, my wife and I, we are together since we are teenagers. All of our lives and both kids are from us and that's it.... she doesn't show any emotion or anything like that. (Husband)

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Well, I was lonesome of course. I mean that was the main thing, but I was relieved. I mean we would go into the front room and sit down and she'd ask me who I was and I said, 'Well, I'm your husband.' . . . she didn't even recognize this house as her home, and we planned it and had it built, landscaped It and all of that. (Husband)

With an adult child who is already juggling many responsibilities, there is more a bewilderment process with behavioral changes in the AD progression and certainly guilt with placement. The children say while you expect to lose a parent eventually and the process is painful, with the severe behavioral changes there comes a role reversal in their dependent-independent relationship. When they take away their parents' independence with placement, they feel guilt. This is true even when absolutely necessary for the severest of safety issues. Another issue for the adult child is the need for placement often signals a progression in the disease process. Thus, it may be easier to verbalize the guilt with placement than think about the finality of the loss of the parent.

Another caregiver difference occurs shortly after placement, in the early transition time. The differences in spouse and adult child behaviors might be described as the adult child being more reactive vs the spouse being more accepting. While having an idea of what they desired in a formal care facility prior to transition, after the placement, both caregivers set out to evaluate the quality of care. The spouses often spoke of the facility as an acceptable place, thus appearing to be able to shift pre-placement priorities in order to be able to feel an acceptance with the facility. It was not possible to capture how much of this was tied up in other issues such as the exhaustion level or the desire to find a facility that was close. Certainly clues were given to suggest these issues were relevant. Discussion from these spouse caregivers provides for reflection:

There were times when I thought maybe the care could be better. There were times when I noticed that her hands were, that her fingers were dirty and all, perhaps whatever she had been doing with her hands, they didn't keep her clean in that direction or something like that. But I imagine they took the best care that they could. (Husband)

... he's always -- most of the time he's shaved every day and clean and since he's been bedridden mostly, I'm not real sure about his teeth being brushed. But I really feel that they do a good job on their patients. Like I say, they are caring, they try. (Wife)

An adult child was more likely to move a parent to a different facility rather than look for compromise. This difference was more evident with the focus group discussions than in the individual interviews. Indeed, this adult child response is most likely tied up in the role shift response which was explored earlier. The parent is now in a dependent role and the child, in an effort to respond to this new and increased responsibility, leaves few stones unturned in pursuit of quality of care. On occasion adult children noted the amount of stress they put their parent under, as well as themselves, when making several facility changes. Again, the heavy influence of the role reversal is evident in the guilt with placement, the concern with responsibility to get quality care and the guilt with the toll on their parent for making facility changes. However, after the initial placement evaluation and responses just discussed, there did not seem to be notable differences within the development of the relationship with formal care staff.

This decision brings the caregivers to a shift in their life after placement. To compare the different worlds of the spouse and the adult child after placement is like comparing a major transition with an overall reorganization. This involves a reorganization for the adult child whom goes from a 36-hour day to maybe 12 hours per week. However, the spouse experiences a major transition where their

investment of energy is not that much different but there is a question of where it occurs and what they are doing. For the spouse, there is not only a difference in performance of the caregiving role, but they are still locked into that role. The emotional investment continues for both caregivers. These emotions and interactions involved in being a spouse or adult child are clearly tied to family relations.

### **FAMILY**

The discussion above points to another theme which has operated in many ways throughout these chapters, and that is family. Family is often presented and explored at a social or support level; however, the findings have shown it was not so much an issue of a broader support network as an intense involvement within family relationships and a number of different elements of family. The most fundamental linkage of family is the caregiver-care receiver dyad, but a variety of more extended issues will also be explored.

While families are linked by marriage and birth, there are other variables which enhance this relationship, such as communication, interactions, and sharing a history or reminiscence. What one cannot assume is a poor commitment, lack of attention or neglect will be the outcome from a caregiver who has had a previously poor relationship with the care receiver. Again, this is a very personal and individual caregiving situation.

The caregiving decisions are often made within this family context, even if only as imagined by the caregiver. The caregiver's own sense of self, self worth, accomplishment, and meaning is often not just lodged within the caregiver-care receiver relationship, and not just within their own self-image but also within their ties to that broader family. The responsibilities, the conflicts and that sense of reflected appraisal, i.e., who we are, is done through an imaginary kind of sense of how acceptable our actions would be to our significant others. Even if the impressions are not directly coming out of their family's feedback, it is coming out of the caregiver's imaginings of what they think the family would feel about what they are doing.

One of the issues that has not been recognized as a family theme, both here and in the literature, is the caregiver-care receiver relationship. Basically a family issue, this relationship is often not seen as falling into that side of things but indeed, It is yet another element in the whole question of family relationships. As noted earlier, both Pearlin (1990) and Archbold, et al. (1990) have called attention to the importance of the caregiver-care receiver relationship.

Reflecting the influence of the AD process, the most poignant influence on the caregiver-care receiver relationship is the loss of their past history. All of the interactions and memories gathered over the years are absent for one individual and painfully present for the other. Although all caregivers spoke to this issue, It was especially difficult for spouses from long-term relationships. So, it is not surprising to hear the caregivers speak of loss of the person as well as the reciprocity within the relationship.

Oh well, you've lost the person's -- she doesn't seem to have love anymore. It's a tough situation when you lose a person, that the mind is gone and that's the way it is with some people. (Husband)

Some caregivers experienced another phenomenon that linked the closely shared memories, history and placement decision. It was as if when they placed the care receiver in formal care they sent all the memories along and ended up with a big void. Although by this time the reciprocity was already gone, it was as if the care receiver's physical presence represented the ties to the memories. Thus, the physical presence represented the remaining link to that previously shared relationship.

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So putting her out of my life was a very difficult thing. I hungered too long, but since X (facility) is close to the house, I think we can still be a part of it .... you know, it's a precious person you're trying to do the best for but you can't. Can't do that forever. (Son)

In the caregiver-care receiver relationships, outward behaviors are not indicative of the relationship between the two. Similar behaviors may have different meanings and different behaviors may have similar meanings. The intensity and especially the individuality of the meaning of this relationship is captured in the comparison of the difference in these two adult daughters' relationships with their mothers. Both daughters described almost identical caregiving activities when visiting their mother in the nursing home: much touching, singing favorite songs, reading poetry and brushing their hair. However, the meaning of the behaviors was quite different for each daughter and obviously grounded in their previous relationship.

So my going out there so often is because of the closeness I feel with her .... I want to at least give her as many hugs as I can make her feel like she still has family. . . and I can hug her and kiss her and tell her I love her and all this stuff that I always wanted to do. It's sort of like I'm making up for lost time. And I'm trying to manage something that was broken.

A common response, buried within the caregiver-care receiver relationship, was the worry that somehow the resident would suddenly have a brief touch-point with reality, recognize where they were and realize what the caregiver had done. Obviously, the caregivers live daily with the implications of their decisions, while the care receiver has no overall comprehension of the issues. The fear of this scenario is very real for many caregivers. The following caregiver example captures that description based on the care receiver's perception of a nursing home as where you put someone to die.

I still feel so goddamn guilty about this whole thing, you wouldn't believe it .... I always think, God, what does my wife think of me? . . . Then maybe she has that moment and she maybe realizes that she is in a nursing home, she might think, 'What did my husband do to me?' I Just can't get over that. (Husband)

Although not a point of lengthy discussion but important by its frequency of occurrence and highlighting by caregivers, is the influence of previous family caregiving-caregiver relationships upon this current caregiver-care receiver relationship. While it was noted that some of the care receivers had been caregivers in their earlier life, the most critical influence came within the great number of adult children who had provided caregiving already to another parent. The ability to provide caregiving at home, and successfully by their description, left them feeling they had failed this care receiver.

It wasn't something I had ever wanted. I had intended to take care of her. My father died at home and that's ideal. He didn't have to go to a hospital or nursing home .... We managed. (Daughter)

While the caregivers could share these insights, the topic was too painful to explore in more depth. Thus, it is important to gain insight into, not only the current caregiver-care receiver relationships, but other relationships both the caregiver and care receiver might have experienced in their past. This also suggests, if one is a caregiving type of individual, he or she may get several opportunities in some families.

## EXTENDED FAMILY

Family members are also involved in sorting out their feelings at this time of transition. What the caregiver perceives and how he/she responds is very individualized. The feelings continue to be very intense. If the children or stepchildren agree with the placement decision, it becomes a very powerful reinforcer of a 'good' decision.

But before I put X {wife), X has a daughter, X's my second wife. And she has a daughter that lives up in X (city). And before I put X. in this home, she had come down and we had together inspected a couple of places and she was all in favor of the one that I had selected and when she comes down, she's very happy with what she sees. (Husband)

If, however, there is any conflict surrounding the placement, feelings often run deep and bitter, especially if the family has not shared any caregiving activities and are perceived now to be critiquing or evaluating the caregiving decision.

I thought I was accepted by everybody in this family. For 20 years I thought I was accepted But I found out that day I was simply not and I was gonna do this and I was gonna sign that and I was so upset, so tired, that I signed. . . But they changed so drastically. I suddenly was their step-mother and I suddenly couldn't be trusted. (Wife)

What also happens is, soon after placement, family members often come for a visit after a period of non-involvement and are shocked at the appearance and decline of their resident. They immediately infer that the resident's condition was influenced by the caregiver's lack of attention rather than the result of not only the disease process but their long absence from the resident. This is, unfortunately, true for both spouse and adult children.

..... So they just went out to the nursing home. They have never been there before. It was Sunday. They went in. They couldn't find her. They couldn't find anyone to tell them where she was. And when they did locate her, it was just such a shock because she's lost a lot of weight. . . So, she had lost all this weight, she's tied in a wheelchair. It was a shock to them. (Daughter)

Focus group discussions revealed conflict as well as supportive functions within blended families. It was common to find divorced and remarried care receivers and caregivers as well as stepchildren, half-brothers and half-sisters within the wider caregiving unit. Examples of 'our family' versus 'their family' were often a key issue in both supportive and non-supportive families. The point of reality that this issue touches upon in the caregivers' day-to-day life and decision-making is the challenge of merging several different viewpoints. Open communication and shared perceptions becomes very challenging within these different relationships. Even within a close supportive caregiving system, different family members have different perceptions of a similar event.

I felt like I was committing her to a death camp because -And X (husband), reassured me that it wasn't that at all. She was being placed in a facility where she'd get the kind of skilled care she needed. (Daughter and son-in-law)

However, there are times when siblings and in-laws can be sources of support with difficult deci-

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sions, helping to extend caregiving time at home and seeing caregiving stressors with clearer insights.

Mostly the fact that my brother just said he couldn't go on with it anymore. He was so good for us; he was the only way we could get away. So he would fill in the duty like weekends and all when we would want to do something .... Yeah, well he Just, I think, was more realistic about it. He hadn't lived with her for 30 years. (Son)

I told him (caregiver's sibling), I says, 'X (caregiver) is at the point now where she can smile, she can laugh, she is relaxed, we have conversations again, we go places and do things.' I says, 'I, for one, am not willing to go back to where we were.' .... It Just seems like when her mother went into that care facility, we were given our lives back.

So I told him, 'Gee, X (brother), I would really appreciate it if I take care of mom and dad Sunday if you wouldn't mind coming over Saturday night and doing dinner.' Well since I said that, he never missed dinner Saturday night. He was there every Saturday night with his wife, with his kids, or without them or whatever, but he was there. (Daughter)

Paying for the nursing home costs, although rarely mentioned In the interviews, was identified in the focus groups as a probable source of conflict for families. The financial debate which emerged pitted parental entitlement to care versus taking the parents' savings and providing quality care for them as a responsible way to spend their hard-earned money. Obviously, one plan may leave the kids with some money and the other most likely won't. There was no closure on this debate and again, the outcome is a reminder of the complexity and individuality of the caregiving situation.

Finally, the issue of visiting by grandchildren demonstrated the intergenerational complexities of extended families' involvement in caregiving. This situation emerged as a dilemma for many families. Some saw only the opportunity for the two parties to be together, hoping to build memories for at least the younger generation. Other families saw the potential influence of the nursing home environment with its smells, noises, and above all the behaviors of the other residents as either frightening or inappropriate for the children. One wonders if this is not also reflective of how it seemed for the caregivers themselves, at least in the beginning. The individual most often caught in this situation was the adult child of the protective care-giving spouse. Because they had been sheltered along the way from the decision-making process, they often found this a difficult situation. They are caught in the web of their relationship with both parents, their relationship with their child, and most likely, their relationship with their spouse.

..... the oldest was just 15, and she really had a hard time with that, and the little one, it affected her some, but not as much as the older one. And I think that's the only time that they've been to see X (care receiver/grandfather They ask about him, but they don't seem to want to go again (Wife).

And my, it kind of bugs me but everybody's different. My sister-in-law doesn't want them to see my mother the way she is and that really kinds of bugs me. And that's her right, I guess as a parent, but I Just don't see how she feels that's gonna hurt them to see their grandma. (Daughter)

We've always done it here and you know, had usually a family dinner of some kind at least once a week and so we Just kept right on when he was sick and we've never given it up. ....It's

worth it for the children in the family. (Wife)

Most often, if the grandchildren had been involved with the grandparent during the home care, they remained involved. So, while these behaviors reflect the family focus, the stresses and struggles are felt most acutely by the intimately involved caregiving individual.

Beginning with family at a level in terms of the social level, or within their social integration and social environment, and then later moving to the individual level, is much like the caregiving experience itself. In the early AD process, family often overlook symptoms or change their responses and routines to compensate for changes in the AD individual. Obviously, this results in changes within the caregiving environment, the caregiver-care receiver relationship and the family dynamics. Over time as stress and exhaustion increase, the result is an individual battle by the caregiver for survival.

Finally, the caregiver has been shown not only to be influenced by the relationship with the care receiver but also very affected by the extended family unit in which he finds himself a member. However, how he responds and reacts to these supports and stresses within this family milieu comes down to an individual level and personal survival.

## **SURVIVAL**

Caregivers were quick to point out, if the earlier survival tactics were working, they continued with them over the long term. They found success in recognizing that as they continued to do a good Job in their caregiving role, this positive feeling contributed to their positive perception of self. By now, they had become more sophisticated in their recognition of and avoidance of stressors.

..... I'd try not to go over there when they were trying to feed her or anything like that or I'd go In the afternoon. (Husband)

And there were just a lot of gurgling and moaning and yelling and it was Just really gross. And I thought, my God, how can anybody eat when all you see is this and this is what you're hearing .... What we do now is we just don't go over there during eating times, you know. We either go before or after because it was . . . it'd just gross me out. (Daughter)

The key to dealing with the intense roller coaster effects noted above was to be able to develop strategies. An important first step was to tell themselves it was an OK decision, that it was necessary and timely. In the early adjustments to formal care caregiving they often reviewed how severe the symptoms had become, how sudden the decline had occurred, or how bad the caregiving toll had increased. These insights seemed to help the caregivers accept the stress and guilt of placement. They also planned strategies which allowed themselves to combine a role and a responsibility, i.e., strategize around visiting.

Well I only, I would go about three times a week. I didn't go over there every day. Sometimes I'd go four and sometimes I would go three and sometimes it would be in the morning or .....I'd go in the afternoon. (Husband)

I have a lot of confidence in them. Now with the swing shift, I'm not so sure about that. I was in there several times in the evenings and I don't think it is quite as efficient as it is on the day shift, but no complaints. .... it isn't that you come every Wednesday at a certain time or every

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Sunday, but different shifts, different times, and you see a quality of care there consistently around the clock. (Husband)

If they desired to visit often, they found ways to do this. If visiting was too intense an experience, they looked for signals that it was OK to limit the frequency. The visit was a crucial signal in the caregivers repertoire. For some, it is such a painful a reminder of their loss, they visit only weekly.

.... I go out once a week. I can hardly stand that. And so leaving; not getting, not being with her, but then leaving. Just like turning the blade on the lawn, you know. (Husband)

For others, their loneliness and loss of that daily responsibility find them visiting every day. Don't count out visiting's function of monitoring which is accomplished by observing other resident's care, as well as the status of their own. Also, individuals cannot role model the care or demonstrate the commitment if they never visit.

Yeah, I don't feel good if I don't go see him, even if I drop in for a few minutes, I do there isn't any tears or anything when I leave• But yet, I'm not glad to be leaving• I just feel good that I went to see him. (Wife)

Lastly, it is through those visits over time that the caregiver-staff relationship winds its course. Some caregivers noted a feeling of personal positiveness through now knowing their resident would be able to receive the necessary professional level of care they were unable to provide.

.... so basically I thought perhaps that the nursing home would be a better place for her because they have the facilities, they have the personnel and I just thought it would be better. (Husband)

Others allowed themselves to react to the emotions in the way that felt best to them. Two of the male spouse caregivers provide an interesting contrast.

.... many times, I myself catch myself going 'don't cry, don't cry, don't cry.' I say but then they do come anyway. So when I talk to my sons about it, you know, but I don't think it really affects them that much as it does tome. (Husband)

Well, I suppose I Just turn it off. Bottle it up is what is amounts to, I suppose. (Husband)

Often, a caregiver realized they would be unable to deal with a return to home caregiving and felt at peace with the decision.

.... And I just, you know, once I got away from that, I just felt there was no way I could get, go back to that. And (laugh) I guess I'm selfish but I was so tied in for so long. I just felt like whee (laugh). (Wife)

Survival after placement emerges as a process. The caregiver must not only deal with the loss of the decision-making responsibility and the physical caregiving role, but now must integrate a stranger into this previously intimate and private relationship. Rather quickly, the physical care and the majority of the decisions get transferred to the formal care staff. However, the integrating of the caregiver into that previous one-on-one relationship is a process that requires time and testing. Often

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they begin by developing the ability to ask questions or make suggestions without threatening their resident's care by the staff. Caregivers didn't want to cause problems by being perceived as a trouble-maker for their resident. In other words, much energy goes into avoiding alienation of staff by family caregivers. Realizing this was a major change in their caregiving role, caregivers often recognize the need to allow some time for adjustments to occur.

After being involved in formal caregiving for awhile, two new survival features appeared in the caregivers' move beyond. First, their ability to turn to other residents for meaning in their caregiving and second, the personal self-growth same caregivers discovered in this transition experience. On occasion caregivers confided that the relationship with their resident became too much for a day or two. Often rather than quit going at all, the caregivers turned to other residents with whom they had developed a relationship for a much needed reciprocity. This scenario was described by an adult son:

..... you know she's totally out of it and then you can go and visit someone else and it's sometimes a relief when I don't have to talk to my mother, you know.

Finally, as some of the caregivers described their adjustments to this new caregiving role, they realized it had become a springboard to personal self-growth. They had waged same tremendous personal battles and emerged not only with quality care for their resident, but a high level of self-esteem for themselves. The daughter, who, when she first placed her mother, had to leave part way through the visit to sit in her car and cry before she could return inside, provides a wonderful example. She did this for the first three weeks after placement. Her personal insights to this struggle was described this way:

I had to go back enough times to where I would get used to it or I'm not going back at all because it was Just terrible for me. So anyway, we just kept going back and going back and going back until I could go in there and not get emotional. .... So I really feel good about that and I'm glad that I chose to keep going back as much as I possibly could where I could feel good about it because it's been very hard for me to do that. (Daughter)

Thus, as explored above, surviving can be viewed as a personal issue. However, it is tied up in family issues and spouse-child issues and spouse-child issues are all part of family. While these were the math relationships of the caregiving world at home, the major shift in the transition to formal care comes with the addition of the relationship with formal care staff.

All of the above leads up to them ore individualistic issue of surviving. At some level, surviving sounds individualistic. At another level it is so tied In to all these other factors: the relationship with the care receiver, the relationship with the family, the relationship with formal staff. Thus, the individuals survival is an individual issue but it's bound up in this complex web of relationships that they are trying to guide themselves through during this difficult time in their lives.

### **INDIVIDUALIZED EXPERIENCE**

A critical underpinning of these findings is that every caregiving unit, caregiving family and their care receiver/resident represent a unique and individual experience. Often they get labeled with a name like AD and that frames a progression of symptoms. Also, once the care receiver is placed in a nursing home, it is assumed a homogenization of resident, spouse or adult children caregivers, and extended family member takes place. However, these findings, while windowing in on the difficult and complex interactions and decisions, also support the significant and touching ways these family

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members worked to manage the caregiving responsibilities they assumed.

The benefit of the qualitative approach allowed a glimpse into the real world of the caregiver and the journey from home to formal care. It is obvious from the findings that one cannot talk about the caregiver or care receiver/resident in isolation from one another. Caregiving is commonly treated as on a continuum or linear trajectory, such as might be implied by the phrase, caregiving career. Within this image, one can envision a stage or phase building on or coming after one another. Gubrium (1991) has offered a look at caregiving based on a broader view. Referred to as the 'mosaic of care,' it emphasizes the distinct and complex interpersonal experiences of caring.

However, a mosaic is something that is done on a wall or surface, and made out of pieces or things that are glued or fixed to that surface. Thus, although projecting a complicated pattern, the image projected is very static and very fixed. One can't really grasp it up close, but you have to back off to see how all the little pieces fit together into the larger whole. This would fit with looking more introspectively into the complexity of the caregiving experiences, however, the image remains fixed.

Thus, the author suggests the caregiving process of necessity begs for a kaleidoscopic view rather than a microscopic view. This kaleidoscope contains bits of something within, maybe bits of liquid, crystals or metal pieces. As you turn the kaleidoscope, the bits and pieces change and the pattern shifts and it's literally impossible to go back to the previous pattern once you have shifted. This image suggests interconnections, multiple patterns, pictures, reflections, motion and change. If one thinks about caregiving as patterns of connections and relationships that either help the caregivers move in the direction they need or create a tension that makes it difficult for them to travel on, there is much analogy to the kaleidoscope. As the events, relationships, Alzheimer's disease symptoms, experiences and the caregiver change within their relationship and interaction with one another, the new caregiving result will not be like it has been before. Thus, like similar behaviors meaning something different and different behaviors having similar meanings, each caregiving situation has unique and individual underpinnings.

It is important to assess the fit between the above findings and a framework for practical implementation in formal care. The following summary provides suggestions for professional staff in how they might make use of the findings in planning their caregiving services.

In summary, it is important to recognize these findings do support the caregiving literature's reference to overall physical and often emotional exhaustion in family caregivers. Although exhaustion was common for these caregivers, upon admission to formal care, sensitivity should be directed to the type of caregiver, spouse or adult child. While the spouses may have experienced turning point events around issues of incontinence or safety with their resident, adult children may have experienced a turning point event around behavior changes in their resident. The educated and insightful formal staff caregiver will not assume that spouse and adult children have only the above issue or that even if they do, that the intensity of the event and the significance of the placement decision is similar for each family experiencing this transition. The staff caregiver should ask each family caregiver about their individual experiences and reasons around placement.

In the early staff, family, caregiver interaction it would be helpful to know where the family caregivers are coming from, as well as what they desire in their formal caregiving experiences. Another valuable point of information for better formal care planning is knowing who was involved in making the placement decision. Did the spouse caregiver decide alone? If so, were the children informed and if so, how? If the caregiving adult child included other siblings in the decision-making, were there a broad range of concerns that emerged, directed toward the child caregiver or the formal facility? Might this caregiver need support in the interaction with family members in addition to making the transition to the formal caregiving role?

The key point in the above interactions is the over-time issue. The formal care staff-family

caregiver relationship takes time to build. The above dialogue, as proposed, is enmeshed in the relationship that develops. If anything has been learned from these caregivers, it would be that these relationships take time and are a result of their perceptions, strategies, and trust.

The other key issue is the perceptions of the health care system that the family caregivers bring with them. As they clearly labeled these experiences as either good or bad, a clear question would be appropriate. "What has been your past experience with the health care system?" Since family caregivers gave a clue that they experience an over time adjustment process, staff need to revisit the early identified issues for their continued relevance. Also, knowing that spouse often compromise on their initial placement goals while adult children may move their resident could be useful to the staff. The primary point is that family caregivers can and do change their expectations of the facility after placement.

The findings suggest the family caregivers experience some similarity in adjustment after the decisionmaking and initial placement evaluation. Thus, at this time there seems to be more commonality in the formal care staff-family caregiver relationship. Differences are more attributable to individual uniqueness than type of caregiver. Family caregivers had two key requests, to provide quality of care for their resident and to recognize them as an individual. Embedded in the quality of care issue is a responsibility for both family and staff. For the family member, it was to provide staff clues to the resident as a person and his/her past. For the staff it was to be receptive to the information provided.

It is not uncommon in caregiver literature to find quality of care issues, however, these findings do seem supportive of the "family as forgotten client" agenda. Family caregivers gave many clues to the feelings, approaches and survival tactics they experienced in their desire to remain involved in caregiving. Family caregivers experience a life after placement. While many must initially deal with feelings of guilt, it is a very personal issue in how they do this and how long it takes. Staff could benefit from the two findings dealing with survival tactics and caregivers personal development of self-growth after placement. Caregivers gave clues to visiting and interaction with other residents as clues to their survival tactics. Staff might look for patterns or other clues before they assume the family member who visits only once a week is disinterested or wishes to remain uninvolved. If the family caregiver chooses to reflect on their past caregiving struggles and decisions and to explore ideas about their new found time, staff can also be supportive in their process. A critical underpinning remains, while surviving sounds individualistic, at another level it is tied to the caregivers relationship with the resident, extended family and the staff. Therefore, it is incumbent upon staff to remember each caregiving situation is unique. Similar behaviors can have different meanings and different behaviors can have similar meanings.

Recognizing, therefore, each caregiving family as unique and individual begs for those health care professionals and the systems who interact with them to make a committed effort to individualize their care.

## Chapter 6

### CONCLUSIONS AND RECOMMENDATIONS

This study has traveled into the world of family caregivers as they experience those final decisions that resulted in the transition of their care receiver into formal care. A return to the research proposal and critique of not only the questions, but the findings, introduces this chapter. An evaluation of Bridges' (1980) model applied to the study findings follows. After noting the limitations of the study, emphasis is placed on sharing what has been learned from this effort. Lastly, recommendations are offered toward the areas of policy, practice, family caregivers and future research.

#### CRITIQUE

In the first chapter, the big picture was explored and the following questions were posed: What do family caregivers of Alzheimer's patients experience as they shift their caregiving from home to formal care? How does caregiving in formal care differ from caregiving at home? And, how do family caregivers perceive the relationship that occurs between families and formal care staff? The close contact with the data has provided both a sense of what the answers are and a much more data-driven, grounded theory sense of what the questions are. Essentially, the original research questions were appropriate and facilitated the rich findings around the caregiver responses to the change in the caregiving site. Being aware of these findings, it is evident additional research designed to follow family caregivers during those last weeks of caregiving at home, through the turning points decisions, and into the first six months of formal care caregiving, would help to confirm and extend the findings.

Exhaustion was an issue that proved to be of extreme influence, but was under-represented in the original questions. While there was an attempt to explore the difference in issues between spouse and adult children, it resulted in a 'tip of the iceberg' outcome. Additional research questions should be directed toward increased understanding of the similarities and differences these family caregivers experience. While this research noted the uniqueness of sons, daughters, husbands and wives, additional research in this area would also be useful. Lastly, the focus on the concept of transition provided the hoped-for depth to capture the events surrounding the caregivers move from home to formal care.

Family caregivers providing caregiving at home are involved in constant and daily decisions. Into these experiences they bring past relationships and history, stereotypes from society, values from their family, family caregiving traditions, and previous interactions with the health care system and other informal sources of support. Arriving at the common state of physical and often emotional exhaustion, caregivers described a turning point event that signaled this was the time for the big decision that would put closure on their ability to provide caregiving at home. The major theme that has been used to organize and examine this material has been the whole notion of transition.

Many writers have worked with different applications of the transition concept. The specific framework that was applied here was Bridges (1980). In applying this model, one of the goals has been to assess how apt a conceptual framework it would prove to be. It was already recognized as an adequate organizing framework, but would it help further the understanding of the transition to formal care? Often within transition, described as change, the role disappears and is replaced by some different role, or there may be a presence of a role versus the absence of a role. For example, in divorce, the role disappears. In caregiving, the disappearance would be analogous to the myth of abandonment. We know this is not true, in the transition to formal care, the role continues but is very highly modified.

### **WHAT WAS LEARNED**

Each family is individual; however, if the range of themes that were identified in this study are applied, it will provide valuable clues about each family in order to see where they are in their lives as caregivers. While we have seen these individuals in all their richness, there is no need to claim that every one is so completely unique they must be studied as an N of one. Instead, broader themes and principles were involved, and if the researcher or clinician starts by looking at those factors, they will project a good idea of where the individual finds himself.

Family turned out to be a very key issue at this point. It was one of those things that seemed like a minor issue in the beginning and turned out to be what everything was tied to. Why did the issue of family end up getting so much more attention? Several findings seem to touch on the answer. First, with AD there is a slow, gradual development of the caregiver responsibility. The caregiver and care receiver bring a shared history and a shared relationship into this experience. Within this 'cast of characters' there is an intimate and personal nature imbedded in the relationships between spouses, parent-child, siblings and extended family. Thus, caregivers can often do the things they do because of the help from the family. At the same time, they often feel pressured to continue because of their perceptions of what the family will think.

Thus, when family caregivers approach decision making, particularly the decisions that end home-based caregiving leading to placement, it is helpful to consider what is involved. These decisions take place in a personal, social, and biographical context as captured in the individual themes of family and surviving. They must wrestle with the caregiving issues per se, the caregiver needs, their ability to continue to caregive and when that final move to formal care must be executed. The magnitude of the range of these bigger issues is always going to be involved in the specific decisions.

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Another point learned from this study centered on the influence of crisis within the decision making process. While the literature often flags the importance of crises, the findings of this study, while not negotiating this, also call attention to the crucial nature of events. The kinds of events turn out to be more like turning points rather than crises. An important difference is that a turning point changes one's understanding of the situation rather than confronts one with a radical shift in caregiving tasks.

The findings called attention to an issue that was not unimportant but relatively straightforward, the Health Care System. By the time the family caregivers were beginning to seriously consider the placement decision, they not only had several experiences but a definite perception of this system as either positive or negative. The perceptions of these past interactions were not only powerful in the placement decision but they continued to significantly influence the early relationships with the formal care staff and facility.

If one was looking for support as a major issue, the findings did not confirm this. It turns out support was a limited notion and may not have that much to do with what is going on at this point in the caregiver's life. Although there was a tremendous amount of attention to family, not all of that family attention was supportive by any means. The question of what is going on in close relationships, not just in exchange of receiving support to meet stress, but what is happening in terms of who people are most intimately tied to and who their actions in the world must depend on and most affect was observed. Although obvious in the caregivers' discussions, this is different from support. So, from the outside, if we look at the literature, support seems to be the issue, but when we listen to the caregivers and hear about their world, it isn't support; rather, it is those crucial, intimate ties that are very much at this point in their lives, in the family.

An exploration of family caregiving would not be complete without reference here to the worlds of the spouse and adult child. For both, caregiving is physically, and often emotionally, exhausting. Spouses tend to hang on until the last possible moment. This is embedded in their relationship with the care receiver. While the loss is overwhelming, it reflects the earlier commitment this generation made to each other and have carried out over a lifetime. Adult children, while also feeling a sense of loss, do expect to lose a parent. For them, having the care and responsibility for a parent is only one of many responsibilities they face daily. Often it is a safety issue or a need for an increased level of care that makes a change necessary. In making this painful decision, there is a role reversal of the dependent-independent role within the parent-child relationship.

Once in formal care, there was overall little difference in the roles assumed by spouse and adult children. Both identify quality of care for their resident and the establishment of a personal relationship with them by staff as their priority issues. Again, tapping into that shared history, their own caregiving experiences and expertise, and the strong influence of family, they chose to monitor and role model care in an attempt to help the staff get to know their resident as a person. They clearly realize the family caregiving role in formal care is dependent upon their development of a relationship with staff. The aide is the staff person most involved in this relationship. Aides are consistently identified by caregivers as most frequently involved in the intimate care of their resident and with whom the family can identify.

One caveat was uncovered here which also supports the application of Bridges' (1980) model. Family spend much more time on the turning point events, making that end decision phase and developing the relationship with formal care staff or the new beginning phase than they do in the neutral zone phase of the actual placement. Indeed, this placement phase is analogous to the idea of a brief 'time out.'

## RECOMMENDATIONS

The lessons learned from this study have relevance for several different domains: at the level of theory development; the level of Institutional policy; the level of clinical practice in formal care; the level of family caregiving behaviors; and the level of future research. Based upon the findings of this study, the following recommendations are offered within each of these domains:

### **Theory Development**

1. Continue to consider different types of caregiver needs rather than a generic approach to caregiving;
2. Consider further exploration of the concept of turning point events in contrast to crisis;
3. Increase the research focus on the past caregiver-care receiver relationship's effect upon the current caregiving situation; and
4. seek to integrate knowledge on the influences of variables of culture, ethnicity, gender, and family structure and lifestyle into future caregiving practices.

Certainly current literature and recent research often speak of the family caregiver as if it is a single entity. However, the findings of this study point to the importance of carefully recognizing the type of caregiver, is a spouse or adult child. These caregivers shared their different journeys to the placement decision and also how unique the early adjustment to formal care could be. There were also strong clues to possible gender differences, within the spouse group especially.

The discovery of the concept of turning point events in contrast to a crisis looms as a high need for further research. Indeed, much remains to be explored if indeed the majority of family caregivers are not experiencing an actual care receiver or caregiver crisis but instead are experiencing similar events around which the placement decision is made. Increased knowledge will not only help us better define and understand this concept it can then lead to increased individualized support and policy decisions for family caregivers.

The importance of better understanding the influence of the past care receiver-caregiver relationship on the current caregiving situation deserves increased attention. The analysis powerfully demonstrated that similar behaviors can have different meanings and different behaviors can have similar meanings. The current resident-caregiver interaction cannot be assumed to provide a clue to the past relationship.

Finally, it is imperative that variables of culture, ethnicity, family structure and lifestyle be incorporated into future family research. Tomorrow's family caregivers will often be single parents, married two or three times with children and step-children, multiracial, and homosexual. Increased knowledge will help us be more responsive to these families' needs. Plus, as we gain more knowledge in this area, we can begin to ask better questions.

### **Institutional Policy**

1. Establish guidelines to enhance ways for families to increase their involvement in formal caregiving;
2. Support policy development that rewards staff and facilities who contribute to a staff-family caregiving team; and
3. Recommend policy that encourages family and staff recognition of the contribution that each other make to the residents care.

At this time in formal care facilities, it seems, as family caregivers perceive it anyway, there are two parallel tracks for family-resident interaction and staff-resident interaction. It isn't that families cannot become involved, however, they perceive they must often take the initiative to make this

happen. Another point family caregivers noted was the institutions lack of recognition for aides in general and exceptional aides in specific.

It must be remembered that the above recommendations result from the perceptions of family caregivers. Research to explore the perceptions of staff regarding family caregivers who remain involved in their resident's care should be undertaken prior to the actual development and implementation of institutional policy.

### **Clinical Practice and Formal Care**

1. Encourage the formal care staff to look for the level of exhaustion each new Alzheimer resident's caregiver brings with admission;
2. on admission, encourage staff to evaluate the caregiver's past experiences with the health care system;
3. encourage staff to recognize short-term as well as long-term family adjustments to formal care caregiving;
4. encourage staff to recognize their role and responsibility in the development of the caregiver-staff relationship; and
5. remind staff that family caregivers are moving from the role of sole or primary care provided to working as a team member.

It was clear, family caregivers bring not only their family history but their caregiver history with them into formal care. Since exhaustion is common to all caregivers, upon admission, a staff question sensitive to this issue would seem to be 1) insightful into past caregiving history as well as 2) supportive of their past individual role as a caregiver. Staff could use information shared at this time to further explore the family member's past experiences with the health care delivery system. Findings from this study strongly point to how important and useful this information can be for formal care staff.

Staff are aware that family caregivers as well as residents experience a change with placement. However, they may not realize how imbedded it is in making the role change from primary care provider to working as a team member. Recognizing this knowledge and realizing they have a professional responsibility to the family, they would take the initiative to help family members make this transition to formal caregiving. These family caregivers described early as well as over-time adjustments and staff would be advised to share this information with families early on in the transition interactions with families.

### **Family Caregivers' Behaviors**

1. Take responsibility to contribute to positive staff-family interaction;
2. continue to monitor to keep good homes good nursing and influence a positive level of care for their resident;
3. recognize there is a chance for a change in their personal life after placement of their resident, i.e., a move beyond; and
4. encourage individuals to recognize their own unique survival techniques and continue what works for them.

As noted earlier, families often found themselves taking the lead in initiating interactions which they felt contributed to positive staff-family relationships. These caregivers also support earlier research findings that their monitoring helps positively influence the quality of care their family

member receives. They should be encouraged to monitor to keep good homes good.

One might question how families might access this information. Physician and nurse practitioner's offices could benefit by having this information to share with family caregivers as they are counseled regarding the transition to formal care. Support groups would also be an important place to begin. Caregivers should be strongly encouraged to first recognize they will experience changes and then second, to recognize what works for them as they maintain their desired level of involvement in their residents care. Through group discussion, caregivers would be exposed to a variety of different techniques and strategies.

### **Future Research**

1. Design research that will follow the caregiver from home through the actual events, into placement and beyond, to capture the actual transition event and not have to rely on caregiver recall;
2. continue to explore the transition event for the richness and diversity of this experience for caregiving families and their resident;
3. capture the transition experience from the view of the extended family; and
4. repeat this study using a different cohort or generation of family with the focus on blended families and different family lifestyle variations.

It is obvious the findings in this research were based on caregiver recall. A study which followed caregivers from home through the placement decision and transition process could extend these findings and help to increase the knowledge base around families involvement in formal caregiving. Since the findings support the importance of the transition concept and also families' significant ability to influence its outcome, it is important that future research include the extended family in the study of transition to formal caregiving.

### **Summary**

The findings from this research have been well worth the efforts. As noted above, the experiences of spouse and adult child caregivers as they made the transition to formal care caregiving were explored in depth. The caregivers perceptions of the differences between caregiving at home and in formal care identified how hard it was to "hold on while letting go." Finally, an exploration of the major issue in formal care caregiving, that of adding the now-necessary relationship with staff, was initiated. Although a beginning, this area begs for further study.

These findings contribute to the knowledge base about the experiences of spouse and adult children caring for their Alzheimer's family member as they make the transition from caregiving at home to formal care.

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# **ALZHEIMER'S DISEASE AND RELATED DEMENTIAS: ACUTE AND LONG-TERM CARE SERVICES, 1996**

A Report to Congress of the DHHS Advisory Panel on Alzheimer's Disease

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## INTRODUCTION

The United States is undergoing a major shift in its approach to delivering health and social service programs. People with Alzheimer's disease and related disorders (ADRD) are likely to be affected by these developments. In addition to a re-evaluation of the role of government, at all levels, in delivering (or being responsible for the delivery of) services, at least two other shifts in strategy are occurring to reform the targets of economics, access, and quality. Managed care has been seized as the solution to a series of yet poorly defined problems. Chief among these is the rapidly escalating cost of care. The general belief exists that by combining all costs into a single capitated payment, sufficient management pressure can be brought to bear to contain the growth. Those opposed to managed care raise concerns about the restricted choices imposed and the potential for selective enrollment of participants. At a minimum, there is a strong need to adopt some method of payment that accurately reflects the actual risks of those enrolled. People with ADRD are especially vulnerable because popular belief holds that they are expensive to care for. The enthusiasm for managed care seems to extend to both acute and chronic care. States are turning to such programs as a way to control the rapidly rising costs of their Medicaid programs. If the Federal Government turns over full responsibility for Medicaid to the States, the pressure will increase still further. In the sphere of long-term care (L.C.), there is growing interest in shifting the balance of effort away from the present institutionally-dominated model to include more home and community-based care (HCBC). Such a transition would include the emergence of new hybrid forms of institutional and community care, such as assisted living, which permit better (less institutional) living situations and individually packaged services that respond to client needs. Although no specific programs have been proposed exclusively for people with ADRD, their special needs must be addressed in any potential solutions.

In addition to these newer trends, several issues persist. Demographic changes are leading to a growing number of older women who live alone, who fall near or below the poverty line, and who have little or no access to informal support or care. These women will place increasing demands on formal, publicly funded services. In addition, L.C. continues to rely heavily on informal care. The care from spouses, relatives, and friends and neighbors still represents the bulk of services provided. There is no indication that the 80-85 percent of care usually attributed to this source has diminished, but sociological forecasts regularly warn that changes in this country's social and economic situation threaten the stability of this arrangement. As the large majority of women (the traditional source of informal care) enter the workforce, as marital arrangements become more diverse and less stable, and as the birthrate falls (producing fewer children to provide both economic support and direct care), the prospects of continuing to rely heavily on informal care darken. People with ADRD have historically been cared for by just such sources, to the point where caregiver burden and equity issues have become a regular source of concern.

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As the pressures for more service grow and the enthusiasm for providing it declines, the nagging questions about effectiveness of care will intensify. There is a great need to establish just what kinds of care make a difference. As reflected in an earlier report from this Panel, much thought and effort must be directed to the basic question of what is meant by "a difference" (Advisory Panel on Alzheimer's Disease, 1992). The effect of care can be assessed along various individual dimensions, including such factors as cognition, functional status, affect, quality of life, burden of care, and satisfaction. At a minimum, it is important to distinguish compensatory services (designed to assist with those activities the person with ADRD can no longer do for him/herself) from those aimed at restoring function.

Historical problems of access to care are likely to be exacerbated. Under the present system of a federally administered Medicare program to provide acute care health insurance benefits for virtually all people aged 65 and older, and a State administered, but federally overseen, welfare-based Medicaid program that addresses more L.C. issues, there already is substantial variation in the types and amount of services provided. Some of this variation is geographic. Rural areas usually have a more restricted supply of services than do more urban areas. Some is based on wealth; affluent areas usually offer more than areas of poverty. But much of the difference seems to be based on other factors. For example, Medicare expenditures per enrollee vary by more than a factor of 100 percent across States for a mandated equivalent package of benefits. The spread in Medicaid payments and covered services is even greater. As Federal participation is capped, the variation can be expected to widen dramatically. People with ADRD may be adversely affected as services designed specifically to meet their needs, especially those intended to support the informal care system, are assigned low priority. To the extent that organizations seek to enroll participants, people with ADRD may be shunned under the belief that they will present too great a burden for the reimbursement available, although this assumption is not supported by research.

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Beyond the care burdens associated with ADRD, these patients present special problems in developing a rational approach to care. Caregiving burdens are exacerbated by the nature of the disease, especially for informal caregivers, who often must contend with intimate relations with people who are cognitively deteriorating with no obvious concomitant physical signs. These patients also may be shunned by the traditional care system, which sees them as simply too difficult to manage easily.

From a medical perspective, many ADRD patients are physically well except for their cognitive problems. They may be ignored by the medical community because of a sense of impotence about how to manage them and a misperceived threat of high costs. The care needs of ADRD patients are not a part of the repertoire of most primary care providers.

In a social environment that places increasing emphasis on the importance of consumer choice, diseases like ADRD, which attack cognitive function, make it much more difficult to assess patient preferences or even to determine when a treatment is having a positive effect. Much of the response burden is necessarily transferred to proxies, who may or may not be in a position to accurately reflect the preferences of the patients themselves. Moreover, studies of the utility weights (the relative importance) assigned by others to the potential outcomes of care for people with ADRD suggest that the general population has a lower level of concern for the success of interventions directed toward such individuals compared to services for those deemed cognitively competent (Kane et al., 1986).

In large measure, ADRD remains a family affair. The care and the burdens of the disease mean that families are virtually as much the victims of the disease as the patients themselves. Hence, treatment programs need to address these families, at the same time that such strategies may not be highly valued because of budgetary cuts. The Alzheimer's Association continues to play a major advocacy role for families, and may expand their role

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in the development of clinical care programs and service provision in response to managed care initiatives. Family caregivers at four recent forums sponsored by the California Caregiver Resource Centers, for example, consistently reported that what they wanted from L.C. services was flexibility to meet individual and family needs, consumer choice, accessibility to affordable care, and assurances that there will be continuity of care. Other issues highlighted were caregiver support services, legal/financial concerns, and meeting the needs of an ethnically diverse caregiving population.

### **CURRENT THEMES AFFECTING ADRD CARE**

#### (A) Managed Care

Managed care has been seized as a potential solution to the escalating cost of health care. Managed care combines the familiar insurance function with more direct responsibility for providing the needed care through a defined health care delivery system. Managed care offers some potential advantages for older consumers. It simplifies the current Medicare arrangements by eliminating much of the bookkeeping. It holds out the potential for providing an organized approach to care with the capacity to invest in expertise, structured programs, and a management information system that could minimize iatrogenic complications (such as medication interactions). Such systems also could be used to track patients in order to intervene early in deteriorating conditions or even to screen for potentially correctable problems. Case managers could intervene to prevent the development of major disability and mobilize community resources to provide timely assistance to prevent or delay institutional care.

The incentives created by capitated prepayment should encourage the development of alternatives to reduce the use of more expensive services. Hence, ambulatory services and case-finding would be encouraged where there was evidence that interventions reduced subsequent resource utilization.

At the same time, managed care for older people may respond to some undesired incentives. There is reason to believe that the current Medicare health maintenance organizations (HMO's) have benefited from favorable selection, attracting less ill people (Brown et al., 1993). For example, managed care programs are not anxious to enroll older people whom they expect will require more care, such as people with multiple chronic illnesses or those who need special care. They may include people with dementia in that category.

It is less clear how much of this selection occurred by design and how much by chance. Certainly, marketing strategies have some effect, and benefit policies will encourage different types of people to apply. For example, offering a drug benefit would encourage those with multiple chronic diseases to join, whereas a broad range of preventive services might be more attractive to healthier people. Overall, managed care operations anxious to maximize profits will opt not to provide services as long as the omission does not produce a problem. For older people, this strategy may mean foregoing services that have as yet unproved value. Those services not tested may be assumed to be ineffective.

Growth in managed care among both privately and publicly insured groups also produces a number of inconveniences. Choice of care provider is restricted. Some people may have to give up the physician or hospital with which they are familiar. Some programs may introduce various procedures to reduce the use of specialists, such as waiting lists for a restricted panel of specialists, requiring a formal referral from the patient's primary care physician, or having some form of case manager authorize the visit.

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To date, the track record of managed care serving older people has not been exemplary. Although some Medicare HMO's have developed innovative geriatric programs (Fox et al., 1991), most essentially have done business as usual, with little adaptation to respond to a geriatric clientele (Friedman and Kane, 1993). Indeed, there is some reason to suspect that Medicare HMO's may be reluctant to establish active, visible geriatric programs for fear of attracting too many frail older people. Anecdotal information suggests that managed care organizations may be using more registry nurses for home care and hence reducing continuity of care. A study of Medicare home health care indicated that managed care was associated with fewer visits and poorer outcomes (Shaughnessy et al., 1994).

A few geriatrically-oriented models of managed care have been developed that include at least some efforts to bridge the service gap between acute care and L.C. The two most prominent models are the Program for All-Inclusive Care for the Elderly (PACE), which is a series of replications of a model originally developed by On Lok in San Francisco's Chinatown. The PACE programs serve frail older people, most of whom are covered by both Medicare and Medicaid. They use an integrated approach to care built around a day health care center to emphasize active primary care and creative service packages as a means to reduce the use of acute and long-term institutional care (Kane et al., 1992; Branch et al., 1995). Many of their clients suffer from dementia, to the point where some PACE programs were concerned about enrolling too many clients with dementia.

The second model is the social health maintenance organization (S/HMO). This approach combines the Medicare HMO with a limited L.C. benefit. It features active case management and varying degrees of geriatric programming. The first series of four S/HMO's originally was designed by Brandeis (Leutz et al., 1991). The evaluation of these programs suggests that they had, at best, modest effects on changing the health status of their enrollees (Manton et al., 1994). A second set of S/HMO's has been chartered by the Health Care Financing Administration. These programs will utilize a more intense geriatric approach. They will not be able to control the proportion of enrollees who are severely disabled, but will receive different levels of capitated payment based on the risk of greater utilization of services. The S/HMO's receive 100 percent of the Medicare Average Adjusted Per Capita Cost (compared to the 95 percent other Medicare HMO's receive) and use a special rate cell risk adjustment that pays them more for people who are more disabled (and correspondingly less for enrollees who are healthy). Although there is no specific prohibition against enrollees with dementia, there are no specific S/HMO programs to address their needs.

People with dementia are not likely to be attractive to managed care organizations. They are expected to cost more. They are more difficult to manage. They may require special programs. It is, therefore, unlikely that HMO's will develop programs to recruit such members unless special incentives are created. However, managed care could serve as a useful vehicle to develop coordinated care for people with dementia.

The data available do not support concerns about extra costs. The studies by Hay and Ernst (Hay and Ernst, 1987; Ernst and Hay, 1994) suggest that the added costs involve some one-time diagnostic costs (not applicable to most people already diagnosed) and nursing home care (not covered by Medicare HMO's). There was some modest additional cost (\$375-\$1,200) associated with hospital care, but most of this cost seems to be attributable to delays in discharge associated with placement problems. These issues should be more effectively dealt with in a managed care setting, which has access to case management and the potential for making more efficient arrangements for post-hospital care. Rice and colleagues also found additional hospital costs in about the same range (Rice et al., 1993). They noted substantially increased costs related to institutional care and social services (both not covered by Medicare, although the working definition of home health care under Medicare is broadening). A Canadian study found no increased cost for hospital care. Most of the increased costs were attributable to L.C. services in institutions or in the community (Ostbye and Crosse, 1994). Other older, more confined studies also have shown increases in hospital lengths of stay (LOS), usually associated with care planning difficulties (Fields et al., 1986; Levenson et al., 1990; Saravay et al., 1991). Other studies have found no difference in the rate of hospitalization or LOS for patients with dementia (Ganguli et al., 1993; Welch et al., 1992).

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At the very least, better studies and experimentation around this issue should be encouraged and efforts should be made to establish actuarially sound capitation rates for government (and perhaps private) programs based on the real financial risks presented by clients with dementia.

### (B) Integrating Acute and Chronic Care

As noted, several managed care programs have made at least partial efforts to integrate, or coordinate, acute care and L.C. The two efforts certainly are linked. People receiving L.C. need good primary care; and acute care, especially the hospital, often is the entry point for L.C. L.C. is the component of comprehensive health care in which services are provided to frail elderly and disabled people of all ages and their families to promote or restore health or minimize the effects of illness and disability. Techniques such as case management, which devote extra efforts to coordinating care, can prove effective in controlling the costs of such care by avoiding iatrogenic complications and addressing incipient problems early. In this sense, case management serves not simply a gatekeeping, or resource control role, but becomes an extension of primary care. In the case of ADRD, special planning to be sure that medical problems are addressed promptly can avoid later complications. For example, special attention to medication management to be sure that the right drugs are taken as prescribed and that early signs of adverse side effects are detected can prevent hospital admissions. Prompt attention to issues around discharge planning can prevent extended hospital stays while waiting for resolution of caregiving crises. Conversely, better coordinated L.C., including attention to caregivers, can reduce the need for acute interventions around crises. More individualized care plans, which are based on a better understanding of individual client preferences, may avoid the use of psychoactive drugs that invite iatrogenic complications. A systematic approach to dementia care for nursing home residents, which included activities, guidelines for the use of psychotropic drugs, and educational rounds, was shown in a randomized controlled trial to be associated with a reduction in behavior disorders and less use of antipsychotic drugs or physical restraints (Rovner et al., 1996). Housing arrangements that provide greater levels of independence and privacy likewise may alleviate the need for such medications to control disruptive behaviors.

More effective information systems are needed for patients with dementia and their families, as they move between levels of care. For example, a Cleveland project provides information about ADRD, services, and research, as well as an electronic support group on the Cleveland Freenet.

Cognitive problems can interfere with people's ability to make choices. For example, Joanne Lynn found that some impaired individuals could not understand complex changes in the Medicare benefit she was proposing as part of a tradeoff of acute care for more L.C. (Building Health Systems for People with Chronic Illness newsletter, Vol. 1, No. 1, October 1994, Robert Wood Johnson Foundation).

### (C) Balance Between Community and Institutional Care

For many Americans, access to L.C. services is problematic. Issues of equity of access to L.C. for the dependent elderly focus on the shortage of in-home and community services to support family caregivers. There are wide disparities in the availability and access to community services by geographic region, ethnicity and race, class, and gender (Estes, 1993). Public expenditures for community-based services are relatively small compared to those for nursing home care (O'Shaunessy and Price, 1987). Medicaid, which is the principal source of funding of health care services for low income people, finances mostly nursing home care and was not designed to support a full array of social and other long-term community-based care services. Expenditures for L.C. in 1993 were estimated to be \$74.9 billion for institutional care (\$36.9 billion Medicaid/\$4.8 billion Medicare) and \$32.9 billion for home care (\$7.1 billion Medicaid/\$10.7 billion Medicare). The Administration on Aging (AOA) also provides some funding for HCBC to support some portion of personal care at home.

Although public costs for L.C. are growing, a substantial proportion of the direct costs for this care still are paid "out of pocket," and by far the largest share of the indirect costs of ADRD are borne by families. There is concern that limited access to services or overly burdensome out-of-pocket expenses, such as costs of

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remodeling to accommodate assistive equipment for the functionally dependent, cause many elderly and their informal caregivers to choose institutional placement (Kovar and Harris, 1990). Others, most often widowed and childless older adults with severe dependencies, cannot get the care they need unless they enter a nursing home. A substantial share of community dwelling elderly in need of assistance with one or two activities of daily living (ADL's) or instrumental ADL's need more help than they actually receive (Scanlon, 1988).

While there is consensus that health care reform should include services in and among multiple settings and the plan proposed by President Clinton (the Health Security Act of 1993) included L.C. provisions (Kane and Kane, 1994), no specific plan has yet evolved to meet the diverse and complex needs of all people who require L.C. (Rantz, 1993). People with ADRD, the functionally dependent elderly, and the chronically ill of all age groups are among the most disadvantaged for access to L.C., especially HCBC. This is especially true for those who live in rural areas of the United States; are members of ethnic and racial minorities; or are poor, uninsured, or under-insured.

The National Chronic Care Consortium, a vanguard group of organizations concerned about bridging the gap between acute and chronic care, should be encouraged to direct some of its attention specifically to issues of caring for patients with ADRD. Several issues deserve special attention:

(1) Home and Community-Based Long-Term Care--Home and community-based services usually are planned and coordinated by an agency using employed staff or contractual arrangements. HCBC is different from nursing home care in that services are provided to people living at home or in a homelike environment rather than requiring recipients to be residents of institutions (Miller, 1991).

The objectives of the services are to assist disabled individuals with basic tasks of living and/or to provide relief to their caregivers. HCBC covers a broad range of services that extend from skilled-level, medically related services with professional staff to social support services provided by nonprofessionals or informal caregivers (family and friends). Ideally, the formal (paid) community-based services should complement rather than impede services provided by informal caregivers. About 75 percent of the impaired/disabled elderly living outside institutions rely solely on informal care (U.S. Senate, 1988).

For every person currently receiving institutional care, there are an estimated four more people in the community who require some form of L.C. (U.S. Senate, 1988). By the year 2000, 18 percent of the elderly (over 5 million) are projected to have some impairment that requires the help of others. About 5 percent (1.75 million) of these people will be in nursing homes or other institutions, but a staggering 3.5 million needing substantial L.C. will not be institutionalized. Approaches to this looming problem include: (1) reducing the need for home care by improving the health of older people; (2) providing home care when disability and frailty preclude continued independence and self-care; and (3) improving integration across the total continuum of care, and coordinating different care providers who subscribe to a broad view of health care that includes both medical and social components.

Unfortunately, HCBC often is "piecemeal and patchwork" (Kane and Kane, 1987) and characterized by inaccessibility, poor care, unskilled personnel, high out-of-pocket costs, and inadequate linkages to other services, rather than a comprehensive array of services. Miller (1991) provides a taxonomy of services and caregivers in the HCBC domain including five main categories of services:

- assessment, information, and referral services that include services to help people find and coordinate care.
- health and support services that include medically related home care and personal and custodial in-home care.
- community-based out-of-home services.
- living arrangements representing a continuum of living options that provide assistance services short of institutionalization.

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- integrated systems illustrating an array of services that combine financing and care delivery, including medical and social support services that promote independence and quality of life.

(2) Rural Health Care--Several special groups do not receive adequate L.C. services. For example, minority women, impoverished elders, and those without families are especially disadvantaged. Earlier reports have highlighted the gaps in our knowledge about how ethnic and cultural issues may affect care for ADRD (Advisory Panel on Alzheimer's Disease, 1993). Another large group that faces special problems in responding to the challenges of ADRD is the part of the population living in rural areas. In many rural areas the health care service delivery system is impoverished and fragmented; the health, mental health, and social services cannot support people with ADRD and their caregivers. Many services, such as nutrition, adult day care, case management, and transportation, simply do not exist outside the county seat. Improving accessibility to diagnostic services in rural areas, such as through the development of mobile diagnostic clinics or telemedicine, also is essential to rule out reversible dementias and to establish standardized diagnostic criteria for clinical and research purposes. Followup networks (coordinated by the Area Agencies on Aging) linked to diagnostic evaluation could facilitate the development of statewide ADRD registries, which could enhance epidemiological research efforts and facilitate efficient and standardized collection of data to aid State Governments in planning for future care needs.

Even where chore and companion services are available, rural caregivers have limited access to them because there are few mechanisms for communication and articulation of available services. The cost of long distance telephone calls prohibits some caregivers from inquiring about available services, and there is no central repository for current and accurate information on resources, regulations, etc. Better information/dissemination mechanisms in rural areas could help address the isolation of both patients and caregivers. A diverse array of health care professionals are in short supply in rural areas; most rural nursing homes do not offer the full complement of health care services (e.g., social services, physical therapy). Many home care programs are based in struggling rural hospitals and lack the full range of services needed by people with dementia.

Counseling and mental health services are needed to assist caregivers in dealing with issues of burden, anger, and depression, and in coping with behavioral and emotional manifestations of ADRD. There is some evidence that providing support to caregivers can reduce the incidence of depression and the consequences of such (Mittleman et al., 1995). Outreach programs, based in community mental health centers (CMHC's) serving rural catchment areas, also are needed to provide case-finding and in-home treatment, and sponsor support groups for caregivers and people with dementia.

In a recent survey of 107 rural Iowa caregivers, only 51 percent reported using any community-based services. The average cost to them was \$73 per month, borne largely out of pocket. Caregivers reported being motivated by a religious ethic in their caregiving responsibilities and felt a deep sense of personal satisfaction and growth from the experience. Respondents indicated that they were not interested in resources outside of family and friends, in part because they were concerned that confidentiality would be a problem in their rural communities and that help from agencies would be "too close to charity" (Buckwalter et al., 1995). These values, beliefs, and the stigma associated with the use of counseling/mental health services may account in part for the low use of formal services reported, and deserve further investigation. As part of a study of Ohio's PASSPORT program, a Medicaid waiver program for community-based care, investigators found that more than half the cases they investigated affected a client who was cognitively impaired. Rural clients were enthusiastic about the program and felt that the funding was creating services that reached them (Applebaum, 1995). A current demonstration project sponsored by the Health Resources and Services Administration (HRSA) is testing different types of support and services for ADRD patients and their families.

### (D) "New" Forms of Care for People With ADRD

(1) Special Care Units (SCU's)--SCU's were developed in the 1980's as L.C. settings attempted to better meet the needs of people with dementia and to protect residents without dementia in nursing homes. In addition to

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the growing number of elders, the recognition that people with dementia have different care needs from those who are physically frail, and concern that traditional nursing home care has not been responsive to those needs, families and caregivers have created strong interest in establishing specially tailored care for this group (Ory, 1995). At present about 15 percent of nursing homes, representing approximately 2,500 units and more than 50,000 beds, have a SCU or specialized program for people with dementia. Although there has been a clear pattern of growth in SCU's for the past decade, it is less evident whether that trend now has leveled out. The great diversity among SCU's, together with other conceptual, methodological, and measurement issues (e.g., insufficient sample size, high attrition, lack of rigorously controlled studies, ambiguities in definition and selection of units, difficulties in measuring outcomes in a communication-impaired population, and problems related to assessing change and effect over time), have hindered examination of the influence of SCU's on patients (Ory, 1995). Moreover, these studies may reflect potential sources of bias (Sloane et al., 1995).

The NIA Collaborative Studies Initiative was established to address SCU research from a variety of perspectives. Currently, 10 funded studies are included in this 5-year research consortium with goals of identifying key elements of care and appropriate outcomes, evaluating their effects, facilitating standardization in the definition of SCU's, developing consensus on common data elements, and encouraging cross-site analyses to enhance sample size. Because of setting limitations, most of the collaborative studies use epidemiological methodologies to compare care and outcomes in SCU's versus traditional nursing home units, rather than randomized controlled clinical trials (RCT's). However, RCT's may not always be the best design for evaluating interventions related to the milieu. Many of the studies also examine outcomes related to staff, family, other residents without dementia, and case mix/reimbursement issues.

Family members, providers, and policymakers need to know if SCU's are effective, for whom, and at what cost, if they are to avoid paying more for care that is not truly more "special" or beneficial. Moreover, restrictive regulations could stifle innovation that may enhance functioning and quality of life for residents with ADRD, their families, and staff caregivers (Ory, 1995). As the concept of specialized care moves into other community-based settings such as adult daycare centers and assisted living, it becomes increasingly important to be able to define what makes special care "special," and to articulate the effect associated with different types of specialized dementia care across the entire continuum of care settings. Finally, the "outfall" from the NIA collaborative studies also is expected to increase understanding of related issues in this population such as functional assessment, and to refine methods for assessing small changes over time, standardizing environmental measures, and developing typologies for use in evaluating different care settings (Ory, 1995).

The results of the collaborative SCU studies will need to be reviewed carefully. Likely they will reveal a mixed picture, with some outcomes showing favorable differences and others not. It will be important to identify the components of care that seem to account for observed benefits and to recognize the areas where SCU's are not effective. A critical question will be whether such care can be cost effective (i.e., can the resources currently invested be better used). At a time of tight fiscal pressures, proposals for increased spending are not likely to find enthusiastic reception, especially if the gains are modest.

Despite these good beginnings, more rigorously controlled research is needed on the effects of various interventions in SCU's and community settings and with families. For example, the value of intergenerational programs and opportunities for young people or intellectually intact elders to provide care for patients with ADRD needs to be examined. More work also is needed to enhance conceptual and methodological efforts to evaluate program effectiveness. Promising directions for future research related to special care for people with dementia fall into three major themes: (1) What individual elements of SCU's make a difference? (2) What interventions work? and (3) Expansion of the settings for care.

(2) Home and Community-Based Care--A perceptible shift is occurring in the preferences for the site of L.C. For several reasons, we are witnessing expanded interest in HCBC. Although it is by no means always the case, some see it as less expensive. Others view it as a response to the need to develop alternatives to the medical

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model emphasis in most L.C. facilities, and still others believe it improves quality of care and quality of life. A review of the effectiveness of community-based L.C., a substantial portion of which affects people with dementia, finds a mixed bag of results. Other than meeting unmet needs, the majority of studies failed to show significant positive results (Weissert and Hedrick, 1994). Nonetheless, enthusiasm for community-based care remains high. More research is needed to document these perceived improvements over traditional forms of L.C. (e.g., nursing homes).

New forms of HCBC are being created. These include a range of State licensed and unlicensed residential living environments such as small group homes for the aged, adult foster care, residential care facilities, and assisted living arrangements (Wilson, 1994). At present we have little basic descriptive information about these types of residential care facilities or about the characteristics and needs of the growing number of residents who inhabit them.

Adult Foster Care Homes (AFC's), also known as board and care homes or family care homes, are State regulated, generally small (usually not more than five clients per home) residential sites that provide housing and protective oversight. It is estimated that over 60,000 State licensed AFC's exist nationwide, a high percentage of which provide care to frail elderly clients. AFC's probably provide care to large numbers of older adults with early and middle stages of dementia as well, although the precise number is unknown. Yet, extremely limited information is available about care processes and outcomes for residents with dementia in these settings (Collins, 1994).

One recent secondary analysis of survey data from families of people with dementia begins to provide an indication of perceived quality of care from the perspective of family members (Collins 1994). However, these data are limited by lack of information on the person with dementia (e.g., stage of disease), as well as knowledge of whether or not the AFC's represented in the survey were dementia specific. Overall, family members of people with dementia residing in AFC's reported a high level of satisfaction; 90 percent of family respondents indicated that the care met their expectations; and 66 percent said their loved ones adjusted well, while 7 percent reported poor adjustment. Families reported a higher level of overall care in smaller homes (less than 15 beds) compared to larger ones.

Based on the findings from this preliminary survey, from the families' perspective, it appears that AFC's are a viable residential care alternative for people with dementia, certainly worthy of closer scrutiny for the potential of these settings to provide high quality care in a smaller, more homelike environment. Of course, family satisfaction is only one of many outcome measures that need to be examined. The answers to the questions of for WHOM (in terms of older adults with dementia) these settings are best suited, WHEN in the dementia continuum they work best, and HOW dementia care is and should be provided await further research (Collins, 1994).

An analysis of the regulation of board and care homes suggests that much of this care (including assisted living) is unlicensed (Hawes et al., 1995), although there are approximately 34,000 licensed board and care homes with more than 613,000 beds. The report calls for improvements in quality through licensure with or without heavy regulation, and indicates that broad State regulation and licensure of board and care homes may be necessary to improve the safety, quality of life, and quality of care. For example, the report indicates that 40 percent of board and care residents are cognitively impaired and 41 percent are on major psychotropic medications without adequate medical or nursing monitoring. Licensed homes were found to provide more supportive services, operator training in care of the elderly, and less use of psychotropic drugs and medications contraindicated for use in the elderly than unlicensed board and care homes. Extensive regulation and licensure did not appear to affect the proportion of professional nursing staff, knowledge of care procedures and appropriate monitoring of health conditions, or more "cosmetic" features such as availability of physical amenities and attractiveness of the homes.

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A recent report on State statutes and regulations for Assisted Living (Mathews and Mathews, 1995) noted that at least 86 different titles were used to classify these facilities nationwide, including "residential," "adult," "foster," "family," "boarding," "domiciliary," "home," and "assisted living." In addition, great variation was noted in inspection mandates, the nature of licensure, minimum/maximum number of beds, penalties for violations, and staffing. Only 3 percent of the facilities reviewed in this survey of statutes and regulations described themselves as "dementia-specific."

There also is a lack of Federal guidelines to standardize residential care. State regulations vary widely regarding environmental, programming, and nursing care standards, with minimum staffing ratios ordinarily quite low. Although residential care settings vary in size from small private homes for up to 4 residents to large congregate care facilities for more than 100 residents, all offer assistance/care and share with residents the responsibilities for ADL's. Ideally, the care provided is flexible, resident and family oriented, and intended to optimize individual dignity and enhance health status, functioning, and well-being. The physical environment and design features of the facility should support the functioning of the impaired older adult and accommodate behaviors and diminished abilities (Alzheimer's Association, 1994). It has been suggested (Tanner, 1994) that a residential Alzheimer's disease care facility with an aide to resident ratio of 1:5 can care for even severely cognitively impaired residents, and that desirable program and care planning characteristics include the following:

- a supportive and low stress environment
- services that match the stage of the disease process
- resident care without unnecessary chemical and/or physical restraint
- good support systems for families and staff

The Alzheimer's Association monograph, *Residential Settings: An Examination of Alzheimer Issues*, reviews the range of residential settings. It presents a conceptual model illustrating the many issues that need to be addressed, including: philosophy; practice issues such as admissions, staffing patterns, and training; environmental factors such as a supportive physical environment; macro influences and factors (e.g., regulatory process, public funding, market forces) and micro influences and factors (e.g., regional influences, operator specialization); and outcomes/success indicators. Notable from the health services research perspective is the paucity of information beyond anecdotal provider reports of what is needed for "Alzheimer's-friendly" care to be accessible, affordable, and appropriate in residential facilities.

(3) Assisted Living--Over the last decade, research on L.C. services for people with ADRD has focused heavily on two ends of the L.C. continuum--nursing homes and community-based services. While researchers and policymakers have been investigating these care systems, another segment of L.C.--assisted living--has emerged that is neither nursing home nor community care as it has been previously defined. Defined broadly, assisted living is any group residential program not licensed as a nursing home that can respond to unscheduled needs for assistance. The spectrum of assisted living services includes such diverse options as congregate housing, residential care facilities, and adult foster care homes (Collins, 1994); and the package of services can be tailored according to consumer needs and preferences.

Recently, assisted living has been defined more specifically as a service that combines the nursing home's institutional efficiencies of co-locating many clients with a greater emphasis on preserving the homelike qualities of control over one's personal space. Indeed, many nursing homes violate the elements traditionally associated with culturally and socially relevant definitions of "home," in that residents have little control over whom they live with, who comes and goes in their personal space, and other aspects of the environment such as furnishings and appointments. Assisted living is a model of supportive housing that is growing rapidly because of consumer preferences and costs associated with traditional models of L.C. (Wilson, 1994).

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In assisted living settings, clients are viewed primarily as dwellers in apartment-like settings, where they can exercise all the autonomy that accompanies such a situation. Hence, they can decide whom to admit and when to do things. Families of patients with ADRD often prefer the ability to purchase only those services they need and thus conserve resources. In many cases, essential services tailored to the client's needs can be delivered to the client in his/her dwelling without the heavy travel costs usually associated with home care. In essence, assisted living has the potential to combine the features of home care and nursing home, without some of the liabilities of each (Kane and Wilson, 1993).

At the same time, assisted living is viewed by some as a return to an earlier time when nursing homes provided less sophisticated care and were less intensively regulated. The standards for assisted living should not allow substandard care, but neither can the regulatory mechanisms so restrict care as to recreate nursing home conditions. Accountability must be based on some type of outcomes system that permits innovation while maintaining quality.

The State of Oregon has been a leader in developing standards of assisted living for licensure and evaluation of resident outcomes. In Oregon's model program, residents are entitled to a private apartment, shared only by choice, that includes a kitchen, bath with roll-in shower, locking doors, and temperature control capability. The overall shelter costs are not substantially higher in assisted living than in nursing facilities (Wilson, 1994). Routine nursing services and case management for ancillary services are provided. Most importantly, the orientation of staff toward the residents is to empower them by sharing responsibilities, enhancing choices, and managing risks (Wilson, 1994).

A variety of other approaches to assisted living, including statutory changes, demonstration projects, and rule amendments, have been tried in other States with varying degrees of success. Part of the problem is that there is no agreed-upon definition of what constitutes assisted living, except that it is a form of supportive housing.

Although some claims have been made that people with ADRD, even in advanced stages, can at the very least be as effectively managed in assisted living settings as in nursing homes (Brown et al., 1993), there is as yet no empirical evidence to assess the effectiveness of such care for people with ADRD. A strong case can be made that by providing separate accommodations for clients, assisted living provides a prima facie argument for improving the quality of life for cognitively intact people who may share the same facility with people with ADRD and may offer an environment to allow people with ADRD to function without the need for as many external controls. However, this assumption needs to be tested. Although data show that residents in assisted living facilities in Oregon have a substantial level of disability--84 percent with some mobility impairment, 75 percent requiring assistance with medications, and 63 percent requiring assistance with bathing (Wilson, 1994)--more widespread and systematic evidence is needed of the capability of assisted living settings for managing patients with dementia (and at what stage of the disease process they are most suitable). Wilson (1994) has identified four general issues that have arisen around the assisted living movement, which also should be addressed in the context of people with dementia:

- Who should be served by assisted living?
- What services should be provided?
- How will services be delivered?
- What setting works best for assisted living?

Moreover, the distinction between assisted living facilities and other types of residential care facilities often is unclear. To date, little evaluative research has been conducted on assisted living facilities. There remains a need to develop research-based typologies for assisted living facilities as well as other types of residential care facilities (e.g., board and care, homes for the aged, adult foster care homes) to be able to design and implement credible evaluative studies and to address other concerns, as noted below.

Some observers of assisted living express strong concerns that the lower levels of staffing represent a throwback

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to the nursing home care when Medicaid was first introduced. They worry about the lack of professional oversight and the concomitant potential for resident problems.

(4) Adult Day Centers (ADC's)--The numbers of ADC's have grown from about 15 in the 1970's to more than 3,000, with a projected need for 10,000 centers nationally. Adult day services, which provide daytime care and activities in congregate community settings, are being touted as the "un-nursing home" (Partners in Caregiving: The Dementia Services Program, 1995) and are defining themselves as the "cornerstone of community-based L.C." Two projects funded by the Robert Wood Johnson Foundation, the Dementia Care and Respite Services Program (1988-1992) and the Partners in Caregiving: The Dementia Services Program, still underway, were designed to demonstrate the effectiveness of ADC's in serving people with dementia, while at the same time achieving financial self-sufficiency.

Proponents view adult day programs as a major solution to the need for L.C. alternatives, and bemoan their lack of public awareness (Reifler, 1995). They urge that adult day services become part of any mandated comprehensive service "package" for both custodial L.C. and post-hospital care. Currently, Medicare does not reimburse for ADC, and Medicaid dollars for adult day programs vary from State to State, with some providing adequate reimbursement, while others suffer from insufficient funding, or none at all (Partners in Caregiving: The Dementia Services Program, 1995).

More rigorous evaluation research is needed if adult day programs are to convince policymakers and consumers that they are an essential component of the L.C. continuum. Studies must determine the true costs associated with adult day services, and compare cost and patient clinical outcomes with 24-hour institutional or home care with options such as ADC's as part of an integrated service network. ADC's will have to be able to demonstrate their cost-effectiveness; however, to do so, they must first determine what constitutes "effectiveness" and "good care" for this population, and what appropriate outcome measures, from a lifetime perspective, would be--survival time? quality of life? patient and family satisfaction? family burden? (Partners in Caregiving: The Dementia Services Program, 1995).

Recommendations were set forth from a mini White House Conference on Aging, related to adult day services in the areas of financing/funding; education/public awareness; tax credits/deductions; private sector initiatives; regulations; and research.

## HEALTH SERVICES QUESTIONS

Several important health services research questions, including descriptive/epidemiological and outcomes issues, have emerged from examination of the balance between community and institutional care and the development of new forms of care for people with ADRD. These questions build on the crosscutting research needs identified by Ory and Duncker (1992).

Examples of questions that should be addressed include the following:

- (1) How many people with ADRD currently use various care modalities?
- (2) What is the geographic distribution of each modality of care?
- (3) Does use of one type of care displace use of another?
- (4) Do people with ADRD fare better when they are treated separately (segregated) or integrated with cognitively intact individuals?

Do cognitively intact patients enjoy a better quality of life when housed separately from people with ADRD? Is this effect equivalent in all L.C. settings?

- (5) Which modalities can safely manage people with ADRD at different stages of their illness? Which types of care are most effective in caring for people with ADRD over the course of the disease (increasing cognitive and functional impairments)?

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- (6) What are optimal staff:patient ratios in each of these care modalities? Are these ratios different for people with ADRD?
- (7) What would be the economic effect on hospice of treating people with ADRD in the advanced stages of the disease as terminally ill?
- (8) What are the effects (risks and benefits) of leaving people with ADRD at home without informal care?
- (9) Can outcomes of care be compared across modalities with appropriate adjustments for case mix? Should these outcomes then be used as the basis for regulations? To create more appropriate incentives, can outcomes be used as a basis for reimbursement?
- (10) What type and amount of staff training leads to improved patient outcomes?

### (A) Changing Government Policies

(1) Cutbacks in Medicaid--Government at all levels is looking for methods to reduce its obligations for supporting care. If responsibility for L.C. under Medicaid becomes primarily a State-directed program, the disparities that already exist among States will likely increase. At the same time, States will have greater opportunities to pursue innovative programs. For example, only a handful of States have actively undertaken programs to shift the primary site of L.C. from institutions to the community. Federal waiver requirements have held States to a tight substitution standard designed to prevent the overall growth in program expenditures.

Most States face serious problems with regard to L.C. Medicaid expenditures have become a major component of their budgets and L.C. usually receives the largest share of these funds. They are thus not anxious to increase spending in this area, although demographic forecasts suggest that such a shift is inevitable. Most of the Medicaid L.C. dollars currently flow to nursing homes, which nonetheless regularly complain of being under-funded, especially in light of the ever greater demands made on them by regulatory efforts for better quality. In most States, nursing homes have developed formidable lobbying efforts to argue their case. Hence, any efforts to redirect the balance of care between the nursing home and HCBC are likely to encounter substantial political resistance unless it is done as part of a package to add new resources, which does not seem a likely scenario in an era of budget tightening. Moreover, as responsibility devolves to the individual States, the planning and political process is diffused. No central policies are feasible.

The shift to greater State control inevitably will exacerbate the already large variation in the types and intensity of L.C. services. Today, the level of investment in Medicaid-supported L.C. varies widely. For example, 1992 total annual State expenditures on L.C. per person aged 65 and older ranged from \$2,720 in New York to \$349 in Arizona. State annual expenditures on nursing home care per person aged 65 and older in that same year ranged from \$1,555 in Alaska to \$294 in Arizona.

(2) Training Primary Care Providers--Currently, the modest Federal support specifically targeted at increasing geriatric content in health workforce curricula is being threatened with discontinuation as part of general budgetary reductions. The need for better trained personnel to work with ADRD clients already has been addressed in an earlier Panel report (Advisory Panel on Alzheimer's Disease, 1991). Despite the calls for more and better prepared primary care providers to meet the needs of a growing population of older people (Kane et al., 1980; Institute of Medicine, 1993; Reuben and Beck, 1994), substantial gaps still remain (Reuben and Beck, 1994). In addition to physicians, geriatric nurse practitioners have been shown to be an effective source of care for frail older people (Mezey et al., 1989; Kane et al., 1991; Mundinger, 1994; Shaughnessy et al., 1995). However, little specific training in the diagnosis and management of Alzheimer's disease is offered in general training programs for either medicine or nursing (National Forum on Geriatric Education and Training White Papers, 1995; Stolley et al., 1991).

(3) Boundary Issues--The role of Medicare in providing long-term services has begun to increase as the result of broader interpretations of regulations governing home health care. Medicare-supported home health has come to cover longer stays and hence more visits per recipient (Vladeck and Miller, 1994). But these changes have

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not had a substantial direct benefit on ADRD clients because the initial reason for covering home health care still must relate to an acute problem that is expected to either improve or worsen.

At least one Medicare program, the S/HMO's, is providing some, albeit modest, coverage for L.C. Such a step represents a cross-subsidy for Medicaid because at least some of the care provided under this aegis otherwise might have to be covered by the Medicaid program. As pressures on Medicaid programs increase, they can be expected to look for other opportunities to exploit Medicare services.

At present, Medicaid is more likely to subsidize Medicare than the reverse. Programs designed to provide better or more intensive care to patients in nursing homes, for example, prevent hospitalizations, which are paid for by Medicare. Although one currently operating program, Evercare, uses a Medicare capitated contract to cover both hospital care and medical services for nursing home patients in an effort to reduce hospitalizations, it must rely on either the willingness of nursing homes to provide more intensive care or find some incentive for them to do so (Malone et al., 1993). Better integration of Medicaid and Medicare payments would encourage more creative approaches to integrating the care being supported and may lead to overall savings, as well as addressing current concerns about people with dementia being relegated to the "no care" zone, that is bounced back and forth between services in response to increasing restrictions in Medicare and Medicaid spending (Estes and Swan, 1993).

### (B) Client Preferences and Ethical Concerns

(1) Client Preferences--Although there is increasing rhetoric about the need for more client-directed care, the likelihood of providing such opportunities in an era of constrained resources seems small. Some have used client-directed care as a code phrase for some form of voucher, which would limit the government's responsibility for paying for care. However, even proponents have not made clear just how the government could limit its responsibility short of contracting all care to private providers who would assume full risk. Many fear the consequences of such action, worrying that substantial underservice would result.

Because dementia patients, by definition, have lost their capacity for judgment, they cannot be expected to express strong preferences or to be in a position to assume control of their own care. This may be a particular problem for people without families and those who develop dementia after placement in an institution. Some sort of agents will be needed. Putting money into the hands of family members raises concerns about the so-called "woodwork effect" (i.e., inducing demand). However, many of the fears about creating excessive demand by offering community services have not been borne out by experience (Lawton et al., 1989). Indeed, an important question to be explored is why many supportive services for ADRD patients and their families, which some champion as sorely needed, often go underutilized. Issues related to the effectiveness, accessibility, and other barriers to use of available services deserve further attention. On the other hand, it is likely that offering payment for informal care might induce a demand for service, simply because such a policy offers to pay for what already is being done. Perhaps a demonstration project is most suitable to test the effects of such a strategy.

(2) Ethical Concerns--A question that haunts all discussions of L.C. is the extent to which clients should be empowered to make choices about their care. Although much is said about the need for more client-centeredness and even client control, serious concerns are expressed about the dangers involved in clients (or their agents) making bad decisions. The right to folly is not guaranteed, especially if society retains a residual obligation to deal with the results of a poor choice. Our society has not reached the point where it can act like a private insurance agency, monetizing its obligations to a client and negotiating a fixed payment that absolves it of further responsibility. As a result, we feel a need to protect people from themselves, relying on professional guidance to direct, or limit, choices among those deemed appropriate. The tension between assuring responsible action and offering clients real options persists (Kane, 1994).

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It would be easier to advocate for freer decision-making if the conditions for making good decisions could be met. These conditions include good information about the risks and benefits of each of various options and a clear expression of the values the client places on alternative outcomes as a basis for calculating the options that maximize the most desired events. With most L.C., and especially with regard to ADRD, these conditions cannot be met. An earlier Panel report addressed the problems of assessing the values placed on possible outcomes associated with ADRD (Advisory Panel on Alzheimer's Disease, 1992). The current state of the art does not yield the requisite information base to assess the effects of alternative modalities of care.

The past several years have witnessed growing interest in achieving some form of client control through use of advance directives to guide care when the client can no longer speak for him/herself. These directives usually address the avoidance or discontinuance of life support equipment. Closely related to this topic is the whole role of assisted suicide for people who fear living without their cognitive abilities and the potential for developing programs more akin to hospices, which focus exclusively on improving the quality of life of people with terminal conditions. Here too, because dementia robs individuals of their cognitive faculties, it is difficult to talk about quality of life, or at least to know how to assess success in improving it.

A more generic question involves redistribution of resources. As society perceives a shrinking pool of resources for frail older people, questions can be raised about how best to distribute them. At present, a guiding principle has been to try to match resources to needs; those who need more care should get it. An alternative formulation uses more of a triage approach, which takes into account the likelihood of benefit. Resources are allocated to those who have both a need for them and a strong likelihood of benefiting from them. Under such a plan, those who are severely cognitively impaired and hence have little ability to express their quality of life might receive fewer services to make these resources more available to those who can better appreciate them. Because such a utilitarian doctrine raises major ethical dilemmas, careful analysis and much discussion are needed to examine the pros and cons of such a principle of resource distribution. Earlier reports from this Panel have addressed the need to find better ways to measure the success of different types of treatment for ADRD, both therapeutic and compensatory (Advisory Panel on Alzheimer's Disease, 1992). The Panel's interest in conducting outcomes research in ADRD and broadening our conceptions of outcome assessment is ongoing, including the planning and coordination of a 1996 conference devoted to outcomes and jointly sponsored by the Alzheimer's Association, Agency for Health Care Policy and Research, and the Panel. The conference is viewed as a forum for identification and exploration of conceptual and methodological issues that must be addressed in evaluating the effectiveness of interventions designed to improve the lives of people affected by dementia.

Resource allocation questions extend to distributional issues within ADRD as well. At present, most ADRD care is compensatory rather than therapeutic. That is, the clinical goals are directed at making patients comfortable and reducing stressors associated with the disease rather than seeking some demonstrative improvement in functional state. If services should be allocated on the basis of potential benefit, then those ADRD clients who have the least interaction with their environment should receive only minimal care, freeing resources for those who can appreciate the care more. Such a step would mean pursuing a policy that no longer devotes heavy nursing care to people in a vegetative state, for example, but instead looks for less intensive ways to manage these people humanely. More attention would be redirected to those who were more responsive to their environments in an effort to make those environments more satisfying and less disruptive.

(3) End of Life Concerns--Because ADRD are terminal illnesses, concern should be directed toward ways of best managing the end of life. For those patients who have reached a terminal stage, some form of hospice care may be appropriate. There is some evidence to suggest that levels of patient discomfort and the costs of care may be reduced (Volicer et al., 1994) and quality of life improved (Collins and Ogle, 1994). Further research is warranted on palliative care approaches in ADRD and on the needs of families who provide terminal care in the home.

## MEASURING THERAPEUTIC EFFECTIVENESS

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More work is generally needed to assess the outcomes of care for ADRD patients. The Panel is participating in this effort by preparing a companion document devoted to an exploration of the goals of therapy in ADRD, and the general principles underlying the analysis of therapeutic goals. While work is ongoing to seek specific therapies designed to improve cognitive performance for people with ADRD, most of the current treatment efforts are designed to prevent untoward behavior or to reduce the stresses associated with the disease.

Fogel has identified five patient-related factors that interact to produce behavior problems, given a specific physical and social environment: perception of current situation, level of arousal, awareness of social context and likely consequences of action, capacity for impulse control, and alternative outlets for self-expression (Fogel, 1994). Several categories of end-points have been identified as outcomes to be considered and measured in therapeutic trials and interventions. These include cognition, physical function, social function, pain and discomfort, adverse behaviors, caregiver stress, and quality of life. Additional factors to be considered include management of co-existing medical conditions, avoidance of iatrogenic consequences, satisfaction with services, and involvement of caregivers in care planning.

### RECOMMENDATIONS

The Panel continues to support recommendations originally made in 1992:

- (1) Specific research should be directed toward exploring a wider variety of living situations for people with ADRD and the effects on function and quality of life associated with these varied situations.
- (2) Research on support services for people with ADRD and their families (e.g., respite care) needs to address the issue of "dose-response," including better quantification of both elements, the services provided, and the effects achieved.

In addition, several new recommendations have emerged that would facilitate research, policy development, and public understanding of alternatives to nursing home care:

- (3) State and Federal Governments should adopt uniform language to clearly describe for the public the residential care levels of L.C. services and definitions of residential care based on the type of L.C. services provided.
- (4) Appropriate assessment of the individual resident's needs (which does not place an unreasonable burden on staff and facilities) should be required before entry into all levels of care in the L.C. system, whether publicly or privately financed.
- (5) Create a centralized national database on home and community-based care capable of generating outcomes information to be used in comparing the quality and cost-effectiveness across all types of L.C.
- (6) The L.C. system should allow and encourage older individuals, including those with ADRD, to choose to live in the settings they desire.
- (7) More work is needed to establish actuarially sound reimbursement rates based on the real financial risks presented by clients with dementia.
- (8) Work is needed to assess the relative effectiveness of alternative approaches to L.C. (e.g., assisted living) for ADRD clients.

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(9) To improve rural care, the following recommendations should be considered:

- More training grants to increase the knowledge base and supply of rural practitioners working with people with ADRD and their caregivers.
- More demonstration services grants with rigorous evaluation components to CMHC's, community health centers, and county aging services reaching rural areas to develop, implement, and evaluate multidisciplinary outreach programs for people with dementia and their caregivers.
- Establish and evaluate information/dissemination mechanisms related to ADRD in rural settings.
- Establish and evaluate mobile diagnostic and followup services coordinated by local health care providers with referral to "experts" in remote academic medical centers using innovative technology such as fiber optic networks.

(10) Research on dementia care should address how value differences based on ethnicity, immigration status, race, and religion influence caregivers. Do these factors operate differently in rural compared to urban settings? Do these values change over the course of the illness, and are they different among caregivers in various geographic regions? What outcomes are desired by family caregivers in rural settings? What interventions enhance or maintain positive caregiving experiences in rural caregivers? Are they different than for their urban counterparts?

(11) More research is needed on SCU's with regard to:

- Staff and administrative issues
- Determining which individual elements of programs for caring for people with dementia are most beneficial and cost effective
- Number and type of SCU's on a national basis
- Separating patients with dementia versus integrated care along the continuum of care settings
- Role of SCU's within the L.C. delivery system
- Organization of dementia-oriented practices in other L.C. settings
- Controlled trials of specialized care
- Innovative use of technology for care and training
- Formal staff augmentation through training of volunteers and family
- Abuse/exploitation and poor care of residents with dementia in SCU's versus traditional nursing homes
- Treatment/residential standards, focused differentially on caregiver groups
- Detection and amelioration of depression, pain, anxiety, etc.
- Appropriate levels of care to correspond with disease stage
- Environmental design

(12) More research is needed on dementia care in ADC's with regard to the cost-effectiveness of adult day services, including quality of life for both caregiver/family and client/participant.

(13) More research is needed on dementia care in assisted living with regard to:

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- Outcomes of assisted living compared to nursing home care
- Outcomes and costs of aging in place in assisted living (with additional services provided as needed) compared to transfer to nursing homes
- For which residents with dementia is assisted living more appropriate than nursing homes
- Cost-effectiveness of small facilities versus larger ones
- Effect of regulation on assisted living

(14) Alzheimer's Disease Research Centers should incorporate health services research. Specifically, more information is needed about the patterns of use and related costs for ADRD patients. A longitudinal database combining detailed clinical information with equally precise information about utilization of services would provide a useful basis for many estimations of the fiscal benefits of treatments.

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# **Part 9**

# **Legal Issues**

**Alzheimer's Disease and Related  
Dementias:  
Legal Issues in Care and Treatment, 1994**

A Report to Congress of the Advisory Panel on Alzheimer's Disease

# Alzheimer's Disease

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## Introduction

Alzheimer's disease (AD) currently affects an estimated 4 million Americans. Manifested initially by mild forgetfulness, this devastating disease eventually erodes all cognitive and functional abilities, leading to total dependence on caregivers and, ultimately, to death. The prevalence of AD increases dramatically with age. Persons age 65 to 74 have a 1 in 25 chance of having AD; for those 85 and older, the likelihood rises to a staggering level, approaching 1 in every 2 persons. Those age 85 and over represent the most rapidly growing sector of the American population, portending a dramatic increase in the overall number of cases of AD in the coming decade.

Persons with Alzheimer's disease and related dementias (ADRD) often are unaware of the toll taken by the multiple effects of the disease process at work within them. Initially, they evidence increasing "forgetfulness"; over time, they find themselves unable to work or to manage home life and personal care. Eventually, the inexorable course of the disease leads to loss of cognition and total dependence. On average, an individual's progressive incapacitation, with the attendant dependency and need for family or other forms of care, may last 6 to 8 years (1,2). At times, it can extend decades. In the progression of the disorder, persons with AD lose their ability to make decisions about even the most basic aspects of daily living: when and what to eat; how to dress; how to groom; how to toilet. They become dependent upon 24-hour supervision and need more intensive therapeutic interventions, most often aimed not at the disease itself, but at its secondary behavioral and psychiatric symptoms of agitation, wandering, and inappropriate behavior.

Intervention most often first comes from family and other informal caregivers. The families of those with Alzheimer's disease experience increasingly substantial burdens as the result of the caregiving role. In an effort to delay institutional care, spouses and other family members often attend to the AD patient in the home, at the cost of lost wages, lost jobs, and lost time to tend to one's own needs. The incidence of compromised physical and mental health among family caregivers is significant as well (3). While respite care, adult day programs, and other community-based health care services may help reduce the growing pressure experienced by family caregivers, these services are of limited availability

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in many areas and are not sought by many family caregivers (4).

One of the most common results of this increased caregiver burden is placement in long-term care facilities, adding to the family burden in economic terms. Indeed, AD is one of the late life health problems most greatly feared by American families, due both to the enormous suffering it causes and to the significant costs it incurs. Persons with ADRD often require extended periods of nursing home care; when coupled with their lost income and the lost income of family caregivers, the result may be economic disaster. For many persons with AD, the last years of life are spent in a long-term care facility, the costs of which are borne primarily by today's welfare system (5,6).

In its previous reports, the Panel considered a host of medical, ethical, and health economic issues arising at their interface with Alzheimer's disease. We have examined issues of eligibility, health care financing, and professional training. Panel reports have shed light on the special concerns of ethnic and minority populations facing AD; and we have wrestled with issues of values that control caregiving decisions made by and for persons with ADRD. In this report, we turn to legal issues, another area of growing concern in the care and treatment of AD. Central to the discussion are questions of autonomy and incapacity, medical decisionmaking, and long-term care.

### **The Law and Alzheimer's Disease**

[A] Today, the U.S. legal system contains very little codified "law" specific to Alzheimer's disease and related dementias, notwithstanding the fact that these disorders are thought to affect over 4 million AD patients and perhaps again as many family caregivers and to cost nearly \$100 billion dollars annually. [B] Relatively few statutes, whether at the Federal, state, or local jurisdictional level, contain any reference to Alzheimer's disease itself. A nationwide computer-based research inquiry conducted by the Panel found that in 1993, only 85 Federal and 200 state statutes in any area of jurisprudence included a specific reference to Alzheimer's disease. A preponderance of these statutes provide only for the establishment or operation of government task forces or panels on Alzheimer's disease [C] rather than for the regulation of a substantive area of law. The research query also searched court decisions of record. Of over one half million decisions recorded by this legal computer system, only 260 decisions include any reference to Alzheimer's disease per se. Of these 260 identified cases, 50 contain only passing reference to AD. It should be noted that this figure may be somewhat conservative. A second computer-aided search, using the term senile dementia, a term formerly used to describe what we know today as ADRD, identified an additional 130 cases, again a very small number. The search demonstrates the paucity of legal precedent in the area of ADRD, suggesting also that future decisions or statutes likely will not be based on precedent.

While little statutory, case, or regulatory law deals directly with Alzheimer's disease, a number of general areas of law have a significant effect upon persons with Alzheimer's disease and their families. The balance of this report will focus on those issues, among them legal issues bearing on autonomy and incapacity, and on medical decision-making.

### **Autonomy and Incapacity**

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A fundamental principle of the U.S. legal system is that people [D] are autonomous--entitled to make their own decisions, whether in minor matters such as choosing what to eat, read, or wear, or in major issues such as deciding whether to marry, move from one's home, or refuse medical treatment for a terminal illness. To the greatest possible extent, our legal system supports the concept of self-determination. The legal system begins from the presumption that all persons have both the right and the ability to make their own choices and decisions, so long as those determinations are within the law. This legal presumption remains in effect until a court determines otherwise, [E] based on fact finding and due process.

While legal statutes place a premium on autonomy and self-determination, they also recognize that a range of impairments may render a person incapable of independent decisionmaking, causing them to present a potential hazard to themselves or to others. Physical or mental impairments--among them, Alzheimer's disease or related dementias, stroke, mental illness, developmental disability--may limit a person's capacity to make choices or to undertake activities in one or more areas of life. To respond to questions of impaired decisionmaking ability, our legal system has adopted two separate approaches to the problems that arise in the wake of "incapacity" or "incompetence" [F] (hereafter referred to collectively as "incapacity") to make decisions as the result of that impairment.

First, the legal system has established methods through which persons voluntarily may delegate certain of their decisionmaking rights to others. This arises most often when a risk of incapacity is recognized, such as when a medical diagnosis of a mentally disabling disorder is made early in its course (discussed below in Voluntary Transfers of Decisionmaking). For people who have never been alert (unimpaired) or who, when alert, made no provisions for transfer of decisionmaking, the law provides a second means of transfer. Under this alternative approach, an impaired individual's rights are removed involuntarily and given to another (discussed below in Involuntary Transfers of Decisionmaking).

Critical to the voluntary or involuntary transfer of decisionmaking is the legal determination regarding capacity or incapacity. With either approach, the legal system must establish, through a formal set of procedures, whether a person has the ability to make his or her own reasoned decisions. No single standard has been codified for this legal determination. Rather, the courts broadly look to ascertain whether the person in question understands the basic nature of the decision or decisions being made, reaches his or her decision or decisions in a reasoned manner, and understands the consequences of the determination.

Alzheimer's disease presents particularly complex problems for the legal system in efforts to make determinations of capacity or incapacity. The disease is difficult to diagnose in its early stages. To date, a review of court opinions of record suggests that little, if any, uniformity exists in either how the diagnosis of AD is established or how its severity is measured.

In most of the cases reviewed, the sitting judges simply appear to have relied upon physician or psychologist statements regarding the degree of mental impairment. The testifying expert most often was not asked about past experience or education in working with AD patients. More often than not, the expert appears not to have been asked how the diagnosis was reached. In the few cases in which specific information regarding the diagnostic process was elicited from the expert witness, the diagnosis most often was based upon test scores (usually, the Mini-Mental State Examination--MMSE) and on positron emission tomography (PET) and magnetic resonance imaging (MRI) scans.

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The Panel observes that this approach to the assessment of legal capacity in persons with AD poses a number of problems, including: (a) reliance on a medical evaluation in the absence of specifically identified tests; (b) adequacy of the diagnostic screens, if used; (c) the familiarity of the medical witness with current practices in diagnosis and evaluation of potential AD; (d) reliability of determinations made through an evaluation performed at distinct point in time; and (e) absence of measures of judgment.

From a clinical perspective, the determination that an individual may be suffering from the early stages of AD cannot be made easily or lightly, given its profound consequences for individuals and families alike. For this reason alone, courts should not be satisfied with a suggested diagnosis of AD in the absence of clear medical evidence to support that diagnosis. As will be discussed in greater detail below, even when the diagnosis of AD has been established, a presumption of incapacity would be premature.

While the MMSE and other mental status tests are useful to distinguish normal from impaired cognitive function, they are not necessarily the best tests against which to evaluate the specific cognitive losses and loss of judgment that arise in AD. [G] Research (7) has found that results on this and other similar global measures of mental status may be affected by specific non-cognitive characteristics of the person being evaluated, such as physical health, socioeconomic status, and education. For example, a person with AD who had attained a high level of education may test relatively high on a cognitive screen; yet the score may be low relative to the person's score when healthy. Significant cognitive loss may be present but may not be identified through screening measures since scores from these tests are judged against a scale that has been set to a relatively low common denominator. Similarly, persons with low education may have relatively low cognitive screen scores, but may not be suffering from AD. Moreover, in AD, particularly in its earlier stages, capacity may vary from day to day or even from morning to night; a single test instrument administered on a one-time basis may not reflect the overall state of impairment or lost judgment.

A host of significant diagnostic advances over the decade have led to the availability of more accurate evaluative techniques to aid in the establishment of a diagnosis of AD, whether for use in clinical care or in court-related evaluations of impairment. The Alzheimer's Association, in collaboration with the National Institutes of Health's National Institute of Neurological Disorders and Stroke (NINDS), has developed diagnostic criteria that have been found to have an 80-90 percent accuracy rate, a standard with a higher degree of certainty than found when relying on standard mental status examinations. (A copy of these criteria is found at the back of this report section.) Recent basic research findings suggest that new and more precise tools may not be long in development.

However, even the most accurate measure of lost cognitive capacity or the diagnosis of AD itself provides insufficient information upon which to make a legal determination of lost capacity. [H] The concepts of cognition and judgment--the latter being the focus of the legal proceeding--are not synonymous. In addition to cognitive and neuropsychological assessment, other aspects of judgment should be evaluated through the assessment of occupational capacity or other measures of the practical aspects of functioning. Moreover, in forming a legal opinion of capacity, courts should evaluate historical evidence from the individual in question and informed others (such as family) as well as direct information regarding the individual's ability to make choices, understand the question at hand, and comprehend the outcomes of those choices. Through such means, courts will be able to distinguish more clearly between the loss of memory ("forgetfulness" or early cognitive impairment) and judgment.

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Other difficulties in the legal determination of capacity among persons with ADRD extend to the knowledge base of the medical experts and family of the person in question. The expertise and background of the medical witness, oftentimes a family doctor who has treated the patient for years, may not reflect current knowledge of the diagnosis and treatment of AD. This may lead to untoward findings. For example, one of the primary and early effects of the disease--forgetfulness--does not affect a person's ability to make informed decisions in the early stages of AD; yet evidence of forgetfulness may be central in the legal decisionmaking process. Similarly, family caregivers may have conflicting interests in the outcome, particularly if caregiving has become particularly burdensome to them.

Each of these questions arises in the conduct of a legal evaluation of capacity in a person with AD, without regard to the degree to which the disease has progressed. With the exception of the latest stages of the disease, during which time the individual in question most likely has lost the ability to recognize family or to communicate with any clarity, the questions are no easier to answer. The middle phase of the disease--a period that varies widely from AD patient to AD patient, given the 6-20-year span of the disease--is characterized by significant personality change and loss of judgment and memory, notwithstanding the fact that both speech and mobility remain intact. At this stage, courts and family alike may find it difficult to determine whether an AD patient's decisions are an expression of a desire for continued autonomy, or are a reflection of the disease process itself.

For example, concerned caregivers (family, health care professional, or adult protective services worker) may believe a person with AD to be unable to live alone safely because of the risk of malnutrition, disease, fire, wandering, or other similar hazards resulting from the increased inability to provide self-care or to avoid simple dangers. The person with AD may refuse a move to a supervised living setting, such as a personal care facility or a nursing home. In such cases, a court will be asked to determine whether this person is making a reasoned decision and, therefore, exercising personal autonomy in refusing the move. If the court determines that legal capacity and judgment are present, the person in question will be allowed the risk of self-harm to safeguard his or her personal autonomy. If, on the other hand, the court determines that the person no longer is able to make appropriate decisions, the court will order the person to be placed in the supervised living setting, protecting the person under the state's "parens patriae" or "beneficence" powers.

As discussed in the Third Report of the Advisory Panel on Alzheimer's Disease, the Panel believes that, to the extent possible, the autonomy of a person with AD should be preserved for as long as possible. However, the Panel also recognizes that, at varying times in the course of AD in any one individual, the ability to make decisions, to self-direct daily activities, and to conduct one's life becomes so severely impaired that it becomes dangerous or hazardous to self or to others. While it is the responsibility of the courts to determine the point at which people with AD can no longer continue to act autonomously and decisions affecting their lives must be made by others, the Panel has observed that the information upon which these decisions are made is not necessarily complete or based upon state-of-the-art knowledge of the nature of AD. Moreover, little uniformity exists in how the legal system manages questions of capacity in persons with AD.

For these reasons, the Panel hopes to bring greater assurance of autonomy for the AD patient for the greatest length of time and greater uniformity and clarity to the process of legal determinations of capacity through a number of recommendations:

Current best medical opinion holds that clinical diagnoses of Alzheimer's disease should be

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established through careful clinical evaluation at several different points in time. That evaluation should include, but not be limited to: (a) cognitive screening instruments (such as the MMSE); (b) NINES/ADRDA Alzheimer's screening criteria, including other neuropsychological assessment tools; and © measures of practical aspects of functioning, such as occupational evaluations. In addition, the assessment would be incomplete in the absence of historical evidence provided by the person in question or informed individuals, such as family and personal physician. The same determining procedures and methods should be employed across legal jurisdictions to bring greater uniformity to legal decisionmaking about AD patients' capacity.

Insofar as medical and legal determinations of cognitive ability and judgment are concerned, it is important to separate the two concepts for the purpose of evaluating capacity. Judgment and cognitive ability are not synonymous terms; there is a difference between lost memory and lost judgment. Thus, AD's early feature of memory loss alone does not necessarily compromise a person's ability to make informed decisions or to express preferences; impairment of judgment arises in the course of the disease, not necessarily at its diagnosis. [I] Courts should weigh this distinction carefully in competence determinations. Families and medical professionals, too, should be better informed about these distinctions.

The complexity of capacity determinations for persons with AD suggests that greater uniformity in evaluations and the concomitant need for evaluations at multiple points in time are needed. A person with AD may be competent for certain purposes at a given time, yet found incompetent for other purposes at the same time. [J] For this reason, the Panel recommends that courts consider implementing regularly scheduled reassessments of the legal capacity of persons with ADRD until such time as verbal and communication skills are irrevocably lost, thereby preserving autonomy in as many areas as possible for as long as possible. The Panel concurs that when these skills are determined to be lost irrevocably, repeated determinations of decisionmaking ability no longer are necessary. Given the large number of persons likely to be adjudicated in such a system, states may wish to establish special court diversion programs that utilize a uniform set of criteria and procedures to determine issues of capacity in persons with ADRD.

### Voluntary Transfers of Decisionmaking

All states permit the establishment of voluntary legal arrangements--such as durable powers of attorney and trusts--through which a person can delegate to another the right to make certain decisions on his or her behalf. Historically, such arrangements have dealt primarily with financial matters; more recently, courts have broadened the interpretation of these arrangements to include delegation of broad personal [K] and health care decisionmaking as well.

The most useful of these devices is the durable power of attorney. [L] All states authorize their use for the purposes of delegating authority to manage financial and property matters. Though more than 40 states further authorize their use for purposes of delegating medical and personal decisions, other states make specific and separate statutory provisions for health care decisionmaking. Under a properly drafted general power of attorney, an agent may pay the bills of the impaired person, manage his or her property, provide for the person's dependents, and maintain his or her affairs to protect the impaired person's post-death estate plan. In states that permit powers of attorney to be used for medical and personal surrogate decisionmaking, the agent of a properly drawn power of attorney also may be able to consent to or to refuse medical treatment, hire medical personnel, and decide where the

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impaired person will live. (This last issue may require court approval, particularly for nursing home placement. Statutes vary from state to state.)

Trusts, [N] while more complex and used most often for traditional estate planning purposes, also can provide for the complete management of the financial affairs of an incapacitated person and his or her dependents. Joint asset holdings [O] not a true delegation of authority but a means of sharing "ownership" of funds, may provide a means of simple estate planning and protection against incapacity. Through this mechanism, the healthy owner of a jointly held asset, such as a bank account, may be willing and able to use the assets to pay for the care of the impaired "partner." Unfortunately, this may not always be the case. Thus, this mechanism should be used with caution.

The great advantage of establishing these devices is that they allow a person who may later become incapacitated to determine who will act on his or her behalf. The documents upon which these arrangements are based can provide direction as to the decisions the giver wishes to have made. These devices, when properly drawn or established, generally avoid the need for future court intervention. However, these instruments require advance planning, an activity in which many people do not engage for a variety of reasons. [P] Moreover, the person entering into such advance planning must have the legal ability to make his or her own decision at the time the document is executed. The Panel notes again that a person in the early stages of Alzheimer's disease retains the legal right to make his or her own decisions absent a court finding of incapacity and may well have the current ability to establish voluntary delegations of decisionmaking.

The Panel has found that the use of voluntary transfers of decisionmaking is meager, at best, whether used for the purposes of property and finances or for the purposes of medical and personal decisions. It is unclear whether these devices are not used because people are unaware of them, are unwilling (or emotionally unable) to confront their potential mortality, or perceive them to be too expensive to undertake. Whatever the reason, the Panel believes these voluntary transfers represent an important element in the maintenance of autonomous decisionmaking by persons with ADRD. Decisions made before issues of capacity arise are carried through by others on behalf of the incapacitated person in the manner specified in advance of the loss of judgmental and cognitive capacity. The use of such advance voluntary transfers can help avoid the need for involuntary guardianships once an individual has become incapacitated by AD. For this reason, the Panel makes series of recommendations regarding this issue.

As the Panel found in its third report with respect to persons with AD and as held as a key tenet of jurisprudence for the general population, individual autonomy and the right to make decisions should be granted primacy over the desires of others; these personal rights also should be safeguarded for as long as legally and medically possible. For these reasons, the Panel recommends that the legal and medical communities work together to reach consensus on a specific set of tools through which the legal system may better be able to ascertain whether a person of uncertain cognitive status retains the legal capacity to enter into agreements of any sort, including the legal delegation of decisionmaking. Standardization of these procedures nationwide is indicated, since the incidence and prevalence of AD do not vary widely from state to state. The needs of AD patients in Portland, Maine, are the same as those in Portland, Oregon.

Greater education is needed about the utility and appropriateness of voluntary transfers of authority. Simple descriptions of what these mechanisms are and how they can be undertaken should be provided. Such information should be placed in the context of the nature of ADRD, its course, and

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its potential consequences on individual autonomy and decisionmaking. As discussed in greater detail later in this paper, material on this subject could be included in the larger public education document that the Panel has recommended be developed for dissemination not only by ADRD-related programs, but also by the Administration on Aging through its legal services programs, Area Agencies on Aging, and multipurpose senior centers.

Because persons diagnosed in the early stages of AD often retain the ability to undertake voluntary transfers of decisionmaking, health care professionals working with such persons should provide information about the mechanisms through which such voluntary delegations may be made. This is particularly important in states in which durable powers of attorney may be used to guide medical decisions at later stages of the disease process. From the perspective of the person with AD, the most important aspect of a voluntary transfer may be the early designation of a trusted, knowledgeable, specific surrogate decisionmaker in the event of incapacity. Professional societies, continuing education programs, and medical schools should help educate physicians to issues regarding voluntary transfers, since physicians often represent the most significant contact point for older Americans outside the family structure. In this way, physicians may help assure patient autonomy for as long as possible, ensuring that patient desires are met even when decisionmaking capacity has been lost. The early establishment of a voluntary transfer can safeguard against the need for such determinations at the point of hospital admission, a time not ideal for patient-centered decisionmaking.

### Involuntary Transfers of Decisionmaking

In the absence of a legally binding voluntary arrangement as described above, court intervention is required when a person becomes incapacitated and a decision regarding his or her care or finances must be made. Most often a court's determination that an impaired person has become legally incapacitated is made on a prospective basis; from the moment of the court decision, the impaired person may no longer make decisions that are legally binding. These court actions often are referred to as "protective proceedings," and are divided into two separate categories. When a court determines that a person no longer is able to make personal decisions regarding matters such as where to live, whether to seek medical care (discussed in greater detail below), whether to marry, divorce, or seek other legal action, the court will appoint a surrogate decisionmaker in a guardianship[Q] proceeding. In contrast, conservatorships [R] are legal proceedings to establish incapacity and to identify a surrogate decisionmaker for a person who no longer can manage financial matters such as bill paying, making investments, or selling realty. [S]

Typically, these legal proceedings are brought before the probate or chancery court of the county in which the impaired person lives or owns property. Some variation exists among the states regarding the rights and procedures under which these hearings are convened. However, in general, the court first determines whether the impaired person can still manage his or her personal and financial affairs. If the court finds the person to be incapacitated, it then appoints either a guardian or conservator--or both--to make decisions on the impaired person's behalf. [T]

In the past, courts generally gave guardians and conservators the authority to make all personal and financial decisions on the impaired person's behalf. More recently, however, a growing number of states have adopted laws that permit courts within the state's jurisdiction to restrict the powers to be granted to guardians and conservators, allowing the impaired person to continue to make specific classes of decisions not yet affected by incapacity. At least in theory, such laws support the Panel's

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articulated view that, to the extent practicable and for as long as possible, a person should be entitled to the maintenance of autonomy and self-direction. These laws seem particularly appropriate to persons with Alzheimer's disease, especially in view of the disease's relatively slow progression and the varying degrees of capacity that may be accepted by courts in making capacity determinations about different kinds of decisions. However, in the absence of research, the effectiveness of partial guardianships and conservatorships in the maintenance of personal autonomy is untested.

It is clear to the Panel that the use of voluntary transfers of decisionmaking should be encouraged. Unless the loss of cognition and judgment inherent in a diagnosis of AD is planned for through the exercise of such voluntary legal arrangements, then the courts, not the person with AD, are likely to decide who will become the surrogate decisionmaker and the range of that person's authority.

### **Medical Decisionmaking**

Making decisions about one's own medical matters may be among the most personal of rights. Because the concept of autonomy is at its very roots, the U.S. legal system long has held that patients must be allowed to choose the medical care and treatment that they will receive. Unfortunately, the nature of Alzheimer's disease is such that patients are faced with a diminishing ability to make decisions at the very time that medical interventions are becoming increasingly complex and more difficult for the lay person readily to understand. When working with AD patients over time, health care providers must determine anew at each visit whether the AD patient retains the ability to decide care and, if not, who should be called upon to make decisions on that patient's behalf. The family and friends of the person with Alzheimer's disease are confronted yet again by the nature of the disease and its inevitable progression when they are asked, perhaps for the first time, to make care decisions.

#### The Patient or Presumed Patient

The general rule of law states that a person is presumed legally able to make his or her own decisions until a court determines otherwise. While the presumption may be and has been challenged in court, the law strongly suggests that the benefit of doubt should be given to the patient, thereby preserving the right to decide his or her own care or, in medico/legal terms, to give "informed consent," for so long as an opinion can be expressed. Surprisingly, few court cases have discussed precisely what standards should be used to determine a patient's mental capacity to consent to healthcare. However, the limited case law reviewed by the Panel suggests that the test is whether the patient is of sufficient mind to reasonably understand his or her condition, the nature and effect of the proposed treatment, and the attendant risks in pursuing--and not pursuing--such treatment. Because of our system's preference for autonomy and the very personal nature of the consequences of receiving or refusing medical care, an individual's own decisions about medical care should be given the greatest weight for as long as the patient is able to express a preference.

#### Advance Directives

At a point in time that varies with the speed of the course of disease, a person with AD will become unable to make his or her own medical decisions. Each of the 50 states now has statutes that permittee

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establishment of voluntary arrangements to delegate at least some medical decisionmaking rights to others. These arrangements, referred to as "advance directives," are written documents that patient signs while competent; they direct how health care treatment decisions will be made in the event of future incapacity. Two types of advance directives have been established under law:

A Power of Attorney for Medical Care is a document granting an agent (or "advocate") the right to make some or all medical decisions on the patient's behalf should the patient become ill. All of the states but Alabama have statutes that permit a person to delegate medical decisions to another through a special health care power of attorney or as part of a general power of attorney (discussed earlier in this paper).

A Living Will is a document providing specific instructions to physicians about an individual's wishes regarding medical care in the event the person becomes too ill [U] to articulate such preferences. Forty-eight states have Living Will statutes.

In the new proposed uniform statute, the separate concepts of the living will and the power of attorney for medical care are joined in a single document called an advance directive. That concept has been adopted in statutes in Arizona, Connecticut, Florida, Maryland, New Jersey, Oklahoma, Oregon, and Virginia. These two types of directive often are combined in a single document that contains both a designation of an agent who will carry out the patient's wishes and a set of instructions to physicians who are about to provide care and treatment.

State statutes are not consistent in the delineation of the range of powers that may be given by person in an advance directive. In general, however, such directives may authorize decisions regarding care (selecting who may provide services to the patient), custody (selecting the site at which the care is given), and medical treatment (selecting the diagnostic, surgical, therapeutic, or other procedures provided by health care workers at the differing sites). An interesting issue that may arise in the area of treatment advance directives is the question of experimental treatments for persons who might wish to become research participants. Greater attention should be paid to this last issue, particularly with respect to AD patients, whose loss of legal capacity may occur relatively early in the disease course.

Advance directives can be used and often are used to consent to life-sustaining treatment. They also can be used to refuse life-sustaining treatment at an identified point in the course of an illness; most advance directives are created for this very reason. While all states authorize the creation of advance directives, the extent to which they are actually in use is not known. What research has shown is that surrogate decisionmakers often do not choose the course of action identified as by the patient as preferred. Thus, given the irreversible nature and destruction of cognitive ability inherent in AD, the Panel believes it critical that people express their wishes regarding care: (1) if they have received a tentative or confirming diagnosis of the disorder in its early stages; or(2) if there is any concern about potential future loss of cognitive ability.

### Refusing Medical Treatment

U.S. law now has clarified that individuals have the right to refuse medical treatment in appropriate circumstances. In the *Cruzan v Director, Missouri Department of Health* decision of 1991, the U.S. Supreme Court recognized that the right to refuse medical treatment is protected under the Constitution, although it is not an absolute right without qualification. The Court recognized that states

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do have a legitimate interest in preserving life, preventing suicide, maintaining the integrity of the health care profession, and protecting the rights of minors or other third parties entitled to support and care. These state interests must be balanced against patient autonomy, and often are included in the statutes that permit the creation of advance directives.

In light of these protective but sometimes conflicting interests, states have general freedom to make their own rules regarding treatment refusal. One area in which substantial differences exist among the states is whether the artificial provision of hydration and nutrition falls within the definition of medical treatment, and whether, as such, it then can be refused in an advance directive. In the Cruzan case, the Supreme Court drew no distinction between hydration and nutrition and any other forms of medical treatment, leaving the determination a medical one. Nevertheless, a dwindling number of state statutes continue either to limit or to prohibit the right to refuse such treatment.

Health care providers have expressed concerns that honoring advance directives may result in liability. So far, this concern appears to be unfounded. Advance directive statutes often include provisions that release a provider from civil or criminal liability if a directive has been followed in good faith. Extant court cases do not suggest substantial risk to the health care provider, either. Based on information compiled by the State Justice Institute, only one appellate court case was found to involve criminal charges being brought against a provider for heeding an advance directive; moreover, the charges brought in the case later were dismissed. [V] Similarly, the State Justice Institute review found only a single civil suit brought against a provider for honoring an advance directive; five separate cases have been brought against providers for refusing to honor an advance directive and continuing treatment. [W]

The nature of AD can present problems in the use of advance directives. These devices, whether by statutory language or by drafting, may restrict the right to refuse medical treatment to cases of terminal illness. Family members and others who must act on the patient's behalf find it difficult to know how AD falls within this definition, considering the uncertainty regarding its progression. In the Panel's opinion, AD, today, must be considered a terminal illness; end-stage AD is no less terminal than end-stage cancer or heart disease. The Panel understands that the uniform act on advance directives recently adopted by the National Commissioners of Uniform State Law removes the requirement that end-stage disease be certified. However, until the model statute is adopted by each of the 50 states, the Panel believes that determination of what constitutes "end-stage" AD should be the province of the treating physician. The Panel further suggests that individual physicians, courts, and families should be granted broad permission to establish when an advance directive of a person with ADRD should be honored. Dialogue on this issue is key to successful resolution in the best interests of the patient and society as a whole.

### Treating in the Absence of Advance Directives

When a patient cannot make his or her own decisions and no advance directive has been set in place, health care providers often are uncertain whether they must seek judicial involvement before providing treatment. In some situations, the patient's condition or behavior may make such a step unnecessary. For example, the law long has recognized that informed consent need not be obtained in an emergency. Similarly, consent may be implied when a patient seeks or manifests a willingness to submit to treatment; however, case law does not elucidate clearly the parameters within which these exceptions are legally acceptable. [X]

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In some states, a "family consent" statute further diminishes the need for judicial involvement. In the absence of an advance directive, such a statute typically gives authority to make medical decisions for an incapacitated patient to family members; priority is given to the closest relative.

Reliance on state statutes and court proceedings to determine the appropriateness of medical treatment in the absence of advance directives occurs less frequently than one would suspect by relying on media accounts (e.g., Cruzan, Quinlan, etc.). To date, most frequently, medical decisionmaking for incapacitated people is made informally by families in the absence of specific legal authority or basis for making decisions except their concern and knowledge of the patient's wishes. While this approach may not be supported by clear legal authority, reliance upon family decisionmaking is widespread, not only acknowledged but approved by some courts. [Y] This practice also is supported by the landmark Federal report, *The President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research: Deciding To Forego Life-Sustaining Treatment*, 1983, and is incorporated in many hospital practice guidelines.

When relying upon informal decision makers, health care providers may need to determine who among the family members is the most appropriate to act on the patient's behalf. In most circumstances, the spouse is the preferred first choice. State case decisions often uphold the right of one spouse to act for the other under certain circumstances. The spouse generally also has the highest priority among family members for court appointment as guardian, should legal authorization be sought or required. However, if the spouse is ill or a history of neglect or domestic relations complaints is present, health care providers and courts alike may well question whether the spouse is the best candidate for the role as surrogate decisionmaker.

In the absence of a spouse, adult children generally are the next choice. Unfortunately, the law provides little help in determining which child to rely upon, should there be disagreement between or among them. Again, health care providers should be alert to possible indications of abuse, neglect, or other family difficulties. As the Panel observed in its third report, it is critical to assure against competing interests when it becomes necessary to rely on family or informal caregiver decisionmaking. For this reason, the Panel emphasizes the need for health care professionals to engage in regular conversations about these difficult medical issues with their patients with suspected or diagnosed AD. By placing greater emphasis upon the importance of advance directives, physicians and other health care professionals might help assure that a patient's desires are articulated before issues of capacity arise and long before the need for medical intervention occurs.

### Federal Involvement in Medical Decisionmaking

In 1990, the U.S. Congress adopted the Patient Self-Determination Act, which requires all Medicare or Medicaid certified health care organizations, including hospitals, nursing homes, home health agencies, hospices, and prepaid organizations, to:

1. give all patients written information regarding their rights under state law to make decisions about medical care, including, in particular, the rights to refuse medical treatment and to prepare or have honored written instructions outlining their wishes;
2. have written policies and procedures about the use of "advance directives";
3. include the "advance directive" in the medical record of any patient who has made one; and

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4. educate the facility's staff and the community on issues regarding advance directives.

This law could help increase the awareness and the use of advance directives and not interfere with states' rights to codify state health care law. The statute's laudable goals, however, will be met only if people indeed receive and understand the information regarding their medical decisionmaking rights, and if the means necessary to establish their wishes are readily accessible.

In its Third Report, the Panel identified a number of principles that should guide overall decision-making in the care of AD patients:

Place high priority on the values of patients and families.

Emphasize quality of life, broadly defined, over mere survival.

Encourage resolution of value conflicts among patients, families, and care providers through early education and other mechanisms outside the court system.

The Panel believes that these same principles should guide the medical decisionmaking that occurs in the care and treatment of Alzheimer's patients. To that end and as stated earlier in this paper, the Panel recommends that given the nature and destruction of cognitive ability inherent in AD, people should be encouraged to express their wishes regarding care through the use of advance directives. Such directives are warranted whether the individual is at risk of AD, has received a tentative or confirming diagnosis of the disorder, or if there is any concern about potential loss of cognitive ability in the future.

However, while patient values--expressed through such advance directives--should be foremost in medical decisionmaking, the Panel concedes that much is not known about how individual decisions about treatment preferences may change over time. For example, an advance directive issued in anticipation of AD may be far different from one that might be issued after confirmatory diagnosis of the disorder. For this reason, the Panel believes that greater research is warranted regarding the stability of treatment preferences over time. Such research could help ascertain whether advance directives should be reevaluated and altered at the will of the person with AD at various points in the disease process. Further, by suggesting the use of advance directives, the Panel is also arguing for further basic and clinical research that may lead to the detection of AD in its very earliest stages, before questions that could cloud the validity of an advance directive arise, such as issues of capacity or cognitive status.

Yet, even with an advance directive in place, its utility has been limited by the laws governing such documents. Most often, a right to refuse treatment (contained in an advance directive) is limited to cases of terminal illness. Unfortunately, neither case history nor general practice of medicine or law is clear regarding precisely how AD falls within that definition. In the Panel's view, until such time as the uniform act on advance directives is enacted in each state, both those rendering treatment to OUTPATIENTS and those defining statutes governing the right to refuse treatment today must consider AD to be a terminal illness. End-stage AD should be treated in the same way as end-stage heart disease or cancer; advance directives should be honored based on the treating physician's determination that the illness has reached its final stage. As observed in its previous reports, the Panel recognizes the difficulties inherent in linking such policy principles to clinical care or personal

decisions by individual patients and families. Nonetheless, the issue remains one of values, and those of the individual with AD should remain paramount in the medical and legal decisionmaking processes.

### **Conclusion**

This report represents the culmination of several years of Advisory Panel deliberations regarding legal issues affecting the care and treatment of people with Alzheimer's disease. The issues are complex, ranging from questions of autonomy and capacity to medical treatment and the right to refuse that treatment. The lengthy trajectory of AD further complicates how decisions regarding the legal rights of a person with AD are to be protected and how that person's safety is also to be maintained. The Panel's Third Report emphasized the role of values in the care and treatment of persons with AD. Values form an overarching theme in this report as well, including the values implied in law and statute, the values inherent in the voluntary transfer of decisionmaking, the values held by formal and informal caregivers, and the values contained in advance directives.

The legal implications of Alzheimer's disease have not been clarified in case law to date. However, as the numbers of persons with AD rises, the need for more reasoned and medically sound mechanisms to determine issues of capacity and stage of illness is heightened. To that end, the Panel has made a host of recommendations regarding legal capacity and medical decisionmaking in AD care and treatment.

Medical and legal determinations of cognitive ability and judgment are not synonymous. Courts should weigh this distinction in competence determinations; families and medical professionals should be better informed of the differences.

Greater uniformity in medical evaluations and the conduct of evaluations at different points in time can help ensure that the autonomy of a person with AD may be maintained for as long as possible.

The legal and medical communities should work together to reach consensus on specific nationally applicable tools through which the legal system may be able to ascertain whether a person of uncertain cognitive status retains the legal capacity to make his or her own decisions.

The use and appropriateness of voluntary transfers of authority should be the subject of education for older persons and their families, through not only ADRD-related organizations, but programs working with older Americans in general, whether at the Federal, state, or local levels. Health professionals, too, should be educated about such mechanisms and should provide information about them to their patients or clients. Professional societies, continuing education programs, and medical schools can be helpful in this effort.

The use of advance directives should be encouraged for those at risk of or those diagnosed with AD. Through improved methods of early detection of AD the timely issuance of such directives can be facilitated. Until such time as the model uniform act on advance directives is adopted by each of the states, the use of advance directives, however, must be accompanied by acceptance of the Panel's view that there is such a concept as "end-stage" AD and that the trajectory of AD

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today is no different from that of a patient diagnosed with incurable heart disease or cancer.

The Panel believes that enactment of the recommendations contained in this report will be beneficial not only to large numbers of ADRD patients and their families, but also to the wider community. It calls upon those in the medical and legal professions to begin to grapple with the legal issues surrounding Alzheimer's disease from the perspective of the patient and family, urging greater education of older Americans and caregivers to legal mechanisms available to preserve individual autonomy in the event of lost cognitive capacity due to ADRD.

### Footnotes

[A] -- A computer search of court cases involving persons with AD yielded a variety of topics central to issues of judgment or what, in law, is referred to as "capacity." They included cases that focused on the capacity of a person with AD to marry; to enter into contracts with professionals; to enter into a durable power of attorney; to be tried for criminal acts; to serve as a witness in trials; to be excused legally for failing to act within a required time in the payment of property taxes, in lease renewal, or in response to a court pleading; and to undertake estate planning, such as the preparation of wills or trusts.

[B] -- The National Foundation for Brain Research, which serves as the clearinghouse for Federal activities concerning the Decade of the Brain, has estimated that the total annual costs of dementia in the United States exceed \$113 billion (1991 dollars), with direct costs (medical care, nursing home care) estimated at over \$18 billion, and indirect costs (caregiver time, premature death) estimated at \$94 billion.

[C] -- The few statutes dealing with substantive legal matters demonstrate the difficulties that arise when attempting to draft legislation dealing with a specific illness or disorder in the absence of sufficient knowledge of the disease. Thus, a Utah guardianship statute, for example, requires that the proposed ward in a guardianship hearing be present in the courtroom unless there is "clear and convincing" evidence that the ward is "in the fourth level or stage of Alzheimer's disease." While AD is a progressive disease, clinicians have not adopted any type of system or strategy to identify AD by such "stages," and, thus, would be unlikely to be able to present clear and convincing evidence regarding the "stage" of the disease, notwithstanding the statute's clear wish for them to do so.

[D] -- "Personhood," for the purposes of the law, most often refers to individuals over 18 years of age; some areas of law extend this definition to include minors of mature judgment.

[E] -- Generally, a court's determination that a person no longer can make his or her own decisions is made prospectively in the conduct of a guardian or conservatorship proceeding [discussed in this report under the section Involuntary Transfers of Decisionmaking]. While this determination occurs less frequently, courts may review the past actions of an impaired person and determine that the person lacked the capacity to make a particular decision at the time he or she acted. As a result, the legal effect of the past act is set aside, as in the case of contested wills, questioned gifts, and disputed contracts for goods or services. Such legal challenges most often are brought before probate or chancery court, but, depending upon the nature of the dispute, also may be brought in the general trial courts of a particular locality.

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[F] -- "Incapacity" and "incompetency" are synonymous legal determinations that identify a person as being unable to care for self or property. The terms "incapacitated" or "incompetent" may be used by lay persons and the medical profession to describe someone as functionally or clinically unable to engage in rational decisionmaking. However, insofar as jurisprudence is concerned, an individual is entitled to retain his or her legal right to make decisions until and unless a court of law holds a hearing and makes a legal finding of incapacity or incompetency.

[G] -- Mental status screens play a valuable role in the rapid evaluation of cognitive status; however, in and of themselves, such screens are not adequate for forming a specific diagnostic opinion regarding a particular aspect of cognitive function, such as language, memory, judgment, or psychomotor skills. Since the primary function of screens such as the MMSE is to assess overall cognitive status in a brief and rapid fashion, the screens lack detail about any single aspect of cognition. Detailed assessment requires the use of additional instruments specific to the area of cognition in question. The Agency for Health Care Policy Research Panel on Early Recognition and Initial Assessment of Alzheimer's Disease and Related Dementia [sic] has developed a bibliography containing what researchers and clinicians agree to be the seminal references for ADRD-relevant cognitive screens.

[H] -- Even with the limited number of legal decisions of record involving Alzheimer's disease, number of courts have ruled that a diagnosis of AD alone is insufficient proof that a person is unable to make reasoned decisions.

[I] -- Judgment, too, should be distinguished from personality change, a common symptom in AD, but also present in a number of other disorders. While personality changes may provide indications of potential disease progress, such changes, in and of themselves, are not a proxy measure for judgmental capacity.

[J] -- The law also recognizes that not all types of decision require the same degree of understanding or cognitive capacity. Thus, while a person may be legally unable to make one type of decision, such as a home purchase or the establishment of a financial power of attorney, that person may retain the capacity to make another order of decision, such as writing a will or appointing a medical agent.

[K] -- Certain limits exist regarding the personal rights that may be delegated to another. Clearly, an individual cannot delegate the right to vote or to marry.

[L] -- A power of attorney is a document in which one person designates another to act as his or her agent in certain specified matters. A "durable" power of attorney is one that states specifically that the delegation of authority continues, should the first person become disabled or unable to manage his or her own affairs.

[M] -- All of the 50 states allow medical decisions to be made under either a general durable power of attorney or a specific medical power of attorney.

[N] -- A trust is an agreement in which a person (usually known as the "grantor") gives his or her assets to a "trustee" who, in turn, uses the assets in a manner consistent with the grantor's instructions to care for various "beneficiaries" designated by the grantor.

[O] -- Assets, such as bank accounts, certificates of deposit (CDS), stocks, bonds, real estate, motor vehicles, and the like, can have shared ownership. For assets, such as bank accounts, CDS, and similar

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items, either owner generally has the right to deposit or remove funds. Therefore, by placing a second name on a bank account, an individual may establish a partial protection against incapacity. Upon disability, the second owner may continue to withdraw funds and use them to pay for the first owner's expenses.

[P] -- In the absence of research findings, it is unclear whether this is because people fail to realize the risk of incapacity or the consequences of failing to plan for it, whether people lack access to professionals who may help implement an advance plan (such as attorneys, financial managers, and others), whether people have no reliable agents who can act on their behalf, or whether people fear that engaging in planning somehow may make the feared incapacity more likely to occur (this is called "ostrich" theory).

[Q] -- All states have statutes that authorize a court both to review the personal decisions of person alleged to be incapacitated and to appoint a substitute decisionmaker to act on behalf of the incapacitated person. Such statutes generally are referred to as guardianship proceedings, although nomenclature may vary from state to state.

[R] -- Similarly, each of the 50 states has enacted statutes that authorize a court to review the financial decisions of a person alleged to be incapacitated and to appoint a substitute decisionmaker to act on that person's behalf. In some states, these determinations are incorporated into the guardianship proceedings; in other states, they are handled separately as conservatorships. Again, state terminology and procedure may vary.

[S] -- Federal and state government agencies also provide what, in effect, is a limited "administrative conservatorship." A representative or "third party" payee may be appointed to receive and disburse Social Security, Supplemental Security Income, Department of Veterans Affairs, disability, or other government benefit check for a beneficiary whose disability has affected the ability to manage funds. (The Panel notes that this arrangement is not always the most satisfactory. Problems regarding the management of patient funds by third parties have arisen in a variety of settings in which conflicts of interest arise, most notably in board-and-care facilities.)

[T] -- In states that bifurcate personal and financial decisions, courts frequently will seek or appoint either a guardianship or conservatorship, not both. It is unclear whether such a decision is based on the belief that the impaired person is still able to manage affairs in the other domain of decisionmaking, whether the person already has made voluntary arrangements in the second area, or whether the person simply has no financial or personal needs demanding the appointment of a guardian or conservator.

[U] -- All state living will statutes authorize the use of such directives for "terminally ill" people. Some state statutes further permit living wills to be used for persons in permanently unconscious or persistent vegetative states.

[V] -- *Barber v. Superior Ct of Los Angeles County*, 147 Cal App3 1006, 195 Cal Rptr 484(1983). See *Guidelines for State Court Decision Making in Life Sustaining Medical Treatment cases*, Second Edition, Appendix A, West Publishing.

[W] -- See *Guidelines for State Court Decision Making in Life Sustaining Medical Treatment Cases*, Second Edition, Appendix A, West Publishing.

[X] -- Notwithstanding the latitude, these doctrines do not give health care personnel the right to treat an impaired person contrary to the terms of an advance directive of which they were aware. [Y] -- For example, Quinlan and Rosebush.

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