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Biomedical Advances in Alzheimer's Disease

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Summary

Alzheimer's Disease (AD) is a severely debilitating neurodegenerative condition that currently affects an estimated 4.5 million Americans, with a feasible range of 1.1 to 4.8 million. As the American population ages, the number of people with AD is expected to increase dramatically to approximately 13.2 million affected individuals by 2050 (range: 8.0-16.0 million). Medicare costs to treat a person with AD are almost three times greater than the average for other beneficiaries, and are anticipated to reach $49.3 billion by 2010. Similarly, costs to the Medicaid program could increase from $18.2 billion in 2000 to $33 billion annually in less than 10 years. The recent death of former President Ronald Reagan highlighted not only the challenges of providing health services to an AD patient, but also the devastating impact the disease has on family caregivers.

Since the late 1980s, the dramatic increase in funding for AD research has rapidly expanded our understanding of the disease. However, unlike other important chronic diseases we do not yet have any proven preventive interventions or effective treatments for curing AD. In 1999, at the instruction of Congress, NIH established the AD Prevention Initiative to accelerate basic research and the translation of research findings into clinical practice.

Funding for AD research has been appropriated for many different activities: basic research, clinical research, health services research, and education and training. In addition to budgets that may include funding opportunities for AD research or services, the Consolidated Appropriations Act, FY2005 (P.L. 108-447), appropriated the following amounts to various agencies and projects supporting AD research (subject to the 0.8% rescission adjustment):

- $1.06 billion to the National Institute on Aging (NIA) for aging-related research (NIA spent about $680 million in AD research in 2004);
- $11.8 million to the Administration on Aging (AOA) for AD demonstration programs, $3.0 million for social research into AD care options, best practices and other Alzheimer's research priorities;
- $1.6 million to the Centers for Disease Control and Prevention (CDC) specifically for AD activities.

Consistent with activity in the 108th Congress, early in the 109th a bill was introduced to increase funding for AD research, and to authorize an education and outreach program (H.R. 192, the La Cura Act of 2005).

This report provides an overview of the public health and financial impact of AD, summarizes federal funding for AD research and clinical trials, and discusses our current understanding of AD and promising avenues of AD research. Issues relating to social services for AD patients and support for caregivers are covered in a companion report. This report will not be updated.

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Introduction

Alzheimer's Disease (AD) is a severely debilitating neurodegenerative condition that is currently estimated to affect 4.5 million Americans, though the actual range may be 1.1 to 4.8 million. As the baby boomer population ages, the number of people with AD is expected to increase dramatically to approximately 13.2 million (feasible range: 8-16 million) affected individuals by the year 2050. Medicare costs to treat a person with AD are almost three times greater than the average for other beneficiaries, and are anticipated to reach $49.3 billion by 2010.[1] Similarly, costs to the Medicaid program could increase from $18.2 billion in 2000 to $33 billion annually in less than 10 years. The recent death of former President Ronald Reagan highlighted not only the challenges of providing health services to an AD patient, but also the devastating impact the disease has on family caregivers. The enormous impact will grow as the U.S. population ages.

Since the late 1980s, the dramatic increase in funding for AD research has rapidly expanded our understanding of the disease. However, unlike other important chronic diseases we do not yet have any proven preventive interventions or effective treatments for curing AD. In 1999, at the instruction of Congress, the National Institutes of Health (NIH) established the AD Prevention Initiative to accelerate basic research and the translation of research findings into clinical practice.

The 2005 Omnibus Appropriations Act (P.L. 108-447) appropriated for the following agencies specific amounts for AD research:[2]

- **The National Institute on Aging (NIA)**. Congress appropriated $1.06 billion to the NIA for aging-related research; a large fraction of this total will be devoted to AD research.[3] The conferees further recommended that NIA expand its collaboration with the National Institute of Mental Health (NIMH) as well as the National Institute

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[1] The Lewin Group, "Medicare and Medicaid Costs for People with Alzheimer's Disease," (Washington, DC: Apr. 2001), as cited in Alzheimer's Association, *Alzheimer's Disease: Statistics, 2001*. Medicare's spending does not include nonmedical long-term care supports provided in the community or in nursing homes.

[2] Subject to the 0.8% recession adjustment. Note that these figures are specifically for AD research; appropriations for AD social services are excluded.

[3] In FY2004, NIH reported spending approximately $633 million on AD research, $496 million of which was from the NIA." (Source: CRS personal communication with NIA, July 12, 2005).

for Nursing Research (NINR) on AD to include research related to identifying effective treatments for elderly persons who suffer from depression.

- **The Administration on Aging (AOA)**. In 1998, Congress authorized the Alzheimer's Disease Demonstration Grants to States programs. This program is administered by the AOA, within the U.S. Department of Health and Human Services (HHS). The program's mission is to expand the availability of diagnostic and support services for persons with AD, their families, and their caregivers, as well as to improve the responsiveness of the home and community based care system to persons with dementia. The program focuses on serving hard-to-reach and underserved people with Alzheimer's Disease or related disorders (ADRDs).

In FY2005, Congress appropriated for AOA $12 million specifically for AD demonstration programs. In addition, $3 million was given for social research into AD care options, best practices and other Alzheimer's research priorities that include research into cause, cure and care, as well as respite care, assisted living, and the impact of intervention by social service agencies on victims.

- **The Center for Disease Control and Prevention (CDC)**. Out of CDC's total appropriation of $1.4 billion for health promotion programs, Congress appropriated approximately $1.6 million specifically for AD activities.

Early in the 109th Congress, a bill was introduced to increase funding for AD research, and to authorize an education and outreach program to promote public awareness and risk reduction, with particular emphasis on education and outreach in the Hispanic population (H.R. 192, the La Cura Act of 2005). This bill would significantly increase the NIA budget for AD research to $1.4 billion and would authorize $25 million for demonstration programs.

In the 108th Congress, two hearings on AD focused on defining the short-and long-term biomedical and social implications of the disease and the need for additional research.[4] Several bills were introduced that would have increased funding for research, medical services for patients, or caregiver support.[5]

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[4] U.S. Congress, Senate Committee on Appropriations, Subcommittee on the Departments of Labor, Health and Human Services, and Education, and Related Agencies, *Alzheimer's Disease*, Apr. 1, 2003 (S.Hrg. 108-130), [http://frwebgate.access.gpo.gov/cgi-bin/getdoc.cgi?dbname=108_senate_hearings&docid=f:89018.wais.pdf]. Senate Committee on Health, Education, Labor and Pensions, Subcommittee on Aging, *Breakthroughs in Alzheimer's Research: News You Can Use*, May 11, 2004, [http://help.senate.gov/bills/hlh_42_bill.html].

[5] H.R. 4595 and S. 2533 (the Ronald Reagan Alzheimer's Breakthrough Act of 2004)that would have increased NIH funding for AD research to $1.4 billion in 2005. These bills (continued...)

This report provides an overview of the public health and financial impact of AD, summarizes federal funding for basic AD research and clinical trials, and discusses our current understanding of AD and promising avenues of AD research. Issues relating to other congressional concerns, such as social services for AD patients and support for caregivers, are covered in companion reports.[6] A glossary of terms is included at the end of this report to assist with terminology.

Demographics

New Cases per Year

The incidence of Alzheimer's is estimated at approximately 380,000 new cases per year.[7] In the absence of major medical breakthroughs, experts project that the incidence will more than double to about 959,000 persons per year by 2050.[8]

Current and Future Prevalence

The most recently published estimates (figures being used by the NIA and the Alzheimer's Association) reported that approximately 4.5 million persons were living with clinically-diagnosed AD in 2000.[9] While there has been debate on the exact

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[5] (...continued)
would also have authorized funding for programs supporting family caregivers, lifespan respite care, education of health professionals, and the safe return program. H.R. 3451 (the Alzheimer's Treatment and Caregiver Support Act) would have authorized the Secretary of HHS to make grants available for health care providers to expand treatment services for AD patients, and provide support services for families and caregivers. S. 2029 would have allowed a tax deduction for home health care and adult day respite care for dependents of taxpayers that suffer from AD or related disorder.

[6] See CRS Report RL30664, *Alzheimer's Disease and Caregiver Burden*, by Beverly Johnson and Carol O'Shaughnessy; and CRS Report RL31755, *Family Caregiving to the Elderly by Employed Persons: The Effects on Working Caregivers, Employers, and Federal Policy*, by Linda Levine.

[7] Ronald Brookmeyer, S. Gray, and Claudia Kawas estimated 360,000 in 1997 in "Projections of Alzheimer's Disease in the United States and the Public Health Impact of Delaying Disease Onset," *American Journal of Public Health*, 88(9), 1998 (hereafter cited as Brookmeyer and colleagues, 1998). L.E. Hebert, L.A. Beckett, P.A. Scherr, and D.A. Evans estimated 377,000 in 1995 in "Annual Incidence of Alzheimer's Disease in the United States Projected to the Years 2000 Through 2050," *Alzheimer Disease & Associated Disorders*, 15(4) (Oct./Nov./Dec., 2001). (Hereafter cited as Hebert, et al., *Annual Incidence of Alzheimer's Disease in the U.S.*)

[8] Ibid.

[9] L.E. Hebert, P.A. Scherr, J.L. Bienias, D.A. Bennett, and D.A. Evans, "Alzheimer's Disease in the U.S. Population: Prevalence Estimates using the 2000 Census," *Archives of Neurology*, vol. 60, no. 8 (Aug. 2003). (Hereafter cited as Hebert et al., *Prevalence Estimates.)*

number, experts agree that the range is between 1.1 to 4.8 million.[10] The number of Americans with AD has more than doubled since 1980 and continued rapid growth is expected over the next decades. Some experts project an almost three-fold increase, to 13.2 million by 2050[11] (feasible range of 8.0 to 16.0 million).

Table 1 highlights the wide variation in estimates and projections of AD. The table presents estimates from four major studies carried out by: (1) the Government Accountability Office (referred to as GAO in table; previously known at the General Accounting Office);[12] (2) Sloane and colleagues at the University of North Carolina at Chapel Hill (referred to as Sloane in table);[13] (3) Evans and colleagues at Rush University Medical Center (referred to as Evans in table);[14] and (4) Hebert and colleagues also at Rush University Medical Center (referred to as Hebert and colleagues in table).[15] Estimates of the number of moderate or severe cases are also provided.[16]

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[10] W.B. Grant, "Year 2000 Prevalence of Alzheimer's Disease in the United States," *Archives of Neurology*, vol. 61, May 2004. Grant asserts that the Hebert, et al., Prevalence Estimates over-estimate the prevalence of AD. He highlights a few methodological concerns and notes that research by Brookmeyer and colleagues, 1998, estimated only 2.3 million, with scientific possibility within the range of 1.1 to 4.6 million. In 1998, the General Accounting Office (GAO) judged there to be only 2.1 million cases in 1995, a figure that the Director of the NIA characterized as "substantially lower than those used by NIA and others." One of the main issues contributing to the uncertainty is the lack of definitive diagnostic tests or biological markers of AD, though the accuracy of diagnosis has significantly improved with the development and implementation of diagnostic criteria by NINCDS-ADRDA. U.S. GAO, *Alzheimer Disease: Estimates of Prevalence in the United States*, 1998, GAO/HEHS-98-16. (Hereafter cited as GAO, *Alzheimer Disease: Estimates of Prevalence*.) See also Richard Mayeax, "Epidemiology of Neurodegeneration," *Annual Reviews in Neuroscience*, vol. 26, 2003.

[11] Hebert, et al., *Annual Incidence of Alzheimer's Disease in the U.S.* Estimate is based on assumption that baby boomers will live longer, placing more persons into the older age categories where AD rates are highest.

[12] GAO, *Alzheimer's Disease: Estimates of Prevalence in the United States*.

[13] P.D. Sloane, et al. "The Public Health Impact of Alzheimer's Disease, 2000-2005: Potential Implications of Treatment Advances," *Annual Review of Public Health*, 2002, vol. 23, pp. 213-231.

[14] Denis A. Evans, et al. "The Impact of Alzheimer's Disease in the United States Population," in *The Oldest Old*, ed. Richard M. Suzman, David P. Willis, and Kenneth G. Manton (New York: Oxford University Press, 1995).

[15] Hebert, et al.,*Prevalence Estimates*.

[16] The figures cited in the text as feasible ranges above do not match numbers in **Table 1** precisely for two reasons. First, our analysis included the data and research from additional sources. Second, **Table 1** reports only middle-range projections, and there is greater variability (i.e., a wider range) if the low- and high-range assumptions are used.

Table 1. Four Estimates and Projections of the Prevalence of Alzheimer's Disease, by Stage, 2000-2050
(in millions of cases)

Year	All cases				Moderate or severe cases			
	GAO	Sloane	Evans	Hebert	GAO	Sloane	Evans	Hebert
2000	2.2	2.2	4.8	4.5	1.2	1.2	2.1	2.3
2010	2.7	3.1	5.6	5.1	1.5	2.0	2.5	N/A
2020	3.4	4.1	7.4	5.7	1.9	2.5	3.2	N/A
2030	4.6	5.5	9.7	7.7	2.6	3.4	4.2	N/A
2040	6.3	7.9	11.5	11.0	3.7	4.9	5.3	N/A
2050	8.0	10.2	13.0	13.2	4.7	6.5	6.3	N/A

Sources: CRS compilation based on four research studies.

Notes: Where Hebert et al., *Prevalence Estimates*, use low-, middle-, and high-series estimates of population growth from the 2000 census, only the middle, or most likely, projections are shown here. Projections differ because of both differences in the size of the estimated baseline populations and assumptions about relevant future trends.

N/A= estimates by level 9 of severity are not available in this study.

Age and Alzheimer's Disease

The risk of AD varies significantly by age. The disease is rare in persons under the age of 65. Its onset increases dramatically in each five-year age category above age 65. Of the estimated 4.5 million persons with Alzheimer's,[17] only 0.3 million (7%) were between the ages of 65 and 74 years, 2.4 million (53%) were between the ages of 75 and 84 years, and 1.8 million (40%) were 85 years of age or older.

The *incidence* of AD (new cases) increases dramatically with age — incidence at age 65, for instance, is more than double that observed at age 60 (**Table 2**).[18]

[17] Although the absolute numbers estimated differ across different data sets, the age pattern is always one of increasing incidence and prevalence rates with age. The figures presented are the most recently published, those by Hebert, et al., *Annual Incidence of Alzheimer's Disease in the U.S.* These figures are at the higher-end of the range of plausible estimates.

[18] GAO, 1998, developed through integration of prevalence rates from 18 studies.

Table 2. Alzheimer's Disease: Age-Specific Incidence Rates, United States
(in percent)

Age	Incidence (new cases)	
	Estimate	Feasible range
60	0.08	0.02-0.24
65	0.17	0.05-0.44
70	0.35	0.13-0.82
75	0.71	0.33-1.53
80	1.44	0.71-2.86
85	2.92	1.48-5.33
90	5.95	3.06-9.95
95	12.10	6.36-18.57

Source: R. Brookmeyer and colleagues, "Projections of Alzheimer's Disease in the U.S." *American Journal of Public Health*, 88(9), Sept. 1998, based on four U.S. epidemiologic studies: Framingham, East Boston, Rochester, and Baltimore.

Estimates of AD *prevalence* also vary widely, but experts agree that the pattern is one of sharp increase with age, doubling about every five years over at least the age range of 65 to 85 years (not shown in table). Estimates suggest that, in age group 80-84, about 18% of persons have AD, increasing to 53% of persons by age group 95 and above. Moderate or severe AD is seen in 10% of those aged 80-84 and 35% in age group 95 and above.

Gender and AD

It is often reported that the number of women with AD and the incidence rates for women exceed those of men. However, some experts attribute this to the gender composition of the U.S. population and the longer life expectancy of women, rather than to sex-specific risk factors for the disease.[19]

AD and Co-Morbidity

In addition to AD, patients suffer from many of the same chronic conditions as the non-AD elderly population (see **Table 3**). Some conditions, such as congestive

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[19] Liese E. Hebert, Paul Scherr, Judith J. McCann, Laurel A. Beckett, and Denis A. Evans, "Is the Risk of Developing Alzheimer's Disease Greater for Women than for Men?" *American Journal of Epidemiology* 153 (2) (2001), pp. 132-136

heart failure and cerebrovascular disease are two-three times more common in the AD patients than the general elderly population. Because Alzheimer's disease can complicate co-morbid conditions, the hospital stay for a patient with AD averages longer and is more costly than that of a patient without Alzheimer's. For instance, one study[20] found that the average hospital stay was four days — and $4,000 — more for a patient with dementia than a non-demented person of similar age Dementia also complicates preventable medical situations by impairing patients' abilities to follow medical instructions and manage their own care, and predisposing patients to a two-fold increase in the rates of fractures or other injuries.[21]

Table 3. Prevalence of Co-Morbid Conditions in AD Patients, Adjusted for Age and Gender

Co-morbidity	Prevalence of co-morbidity		
	AD patients	Non-AD elderly	Significantly different?
Cerebrovascular Disease	34.63	10.24	Yes
Congestive Heart Failure	23.94	14.36	Yes
Chronic Pulmonary Disease	19.77	19.96	*No*
Diabetes, Uncomplicated	18.89	16.55	Yes
Peripheral Vascular Disease	14.06	8.71	Yes
Malignancy	10.91	10.04	*No*
Myocardial Infarction	9.66	5.44	Yes
Renal Disease	5.42	3.10	Yes
Diabetes, with Chronic Complications	5.20	3.81	Yes
Peptic Ulcer Disease	4.69	3.38	Yes

Source: H. Fillit, J.W. Hill, and R. Futterman, "Health Care Utilization and Costs of Alzheimer Disease Stage, and Pharmacotherapy," *Family Medicine*, July-Aug. 2002.

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[20] C. Lyketsos, "Dementia in Elderly Persons in a General Hospital," *American Journal of Psychiatry*, 175(5), 2000, as cited in the Alzheimer's Association, *Medicare and Medicaid Costs for People with Alzheimer's Disease*, Apr. 2001.

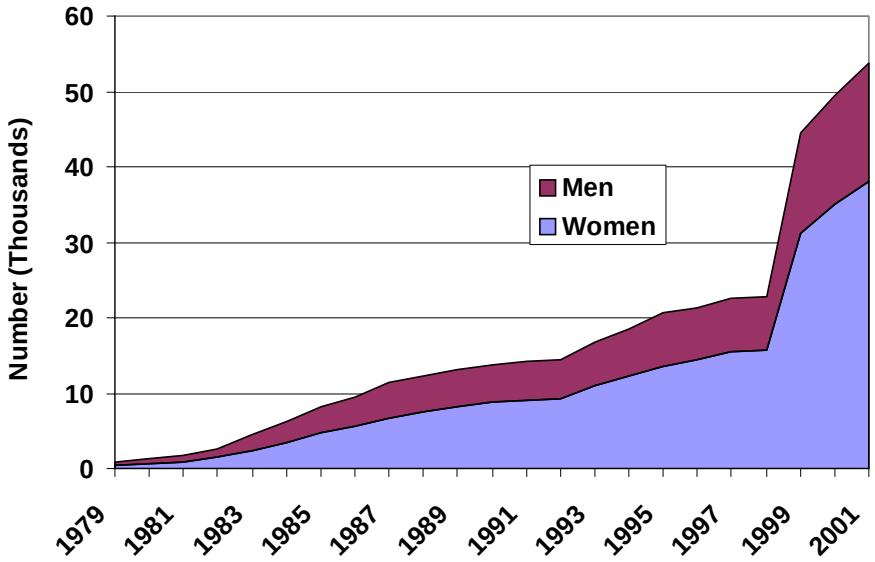
[21] Note that this study was of persons with dementia, a clinical state characterized by loss of function in multiple cognitive domains. There are approximately 70-80 types of dementia, with the most common being Alzheimer's disease. See American Psychiatric Association, *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed. (DSM IV) (Washington, D.C.: American Psychiatric Association, 1994).

AD and Mortality

Fifteen leading causes of death accounted for 83% of all deaths for all ages in the United States in 2001, with deaths from diseases of the heart and malignant neoplasms (with 700,000 and 554,000 deaths, respectively) far out-distancing other causes of death. In 2001, AD was ranked at number 8 as a leading cause of death.[22]

There has been a dramatic increase in the number of reported deaths from AD over the past two decades (**Figure 1**). In 1979, there were only 857 reported deaths from AD.[23] In contrast, AD was reported as the underlying cause of death for a record 53,852 persons in year 2001 (most recent data available), representing about 2.2% of the 2.42 million deaths from all causes.[24] The median survival from initial diagnosis with AD was 4.2 years for men and 5.7 years for women with AD. Men had poor survival across all age groups compared with females.[25]

Figure 1. Alzheimer's Deaths, 1979-2001, by Sex



Source: CRS compilation based on National Vital Statistics data.

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[22] National Center for Health Statistics (NCHS), *National Vital Statistics Reports*, vol. 52, no. 3, Sept. 2003.

[23] This number reflects, in part, lack of awareness of AD generally and unfamiliarity with screening or diagnostic tools.

[24] Official mortality data are compiled through the National Vital Statistics System. The Standard Death Certificate is designed to elicit a single disease or injury that started the morbid process that led to death — referred to as the underlying cause of death.

[25] E.B. Larson, et al., "Survival after Initial Diagnosis of Alzheimer Disease," *Annals of Internal Medicine*, vol. 140, 2004.

In 2001, there were 38,090 (71%) AD deaths in females compared to only 15,762 (29%) for men, presumably reflecting the longer life expectancy of women rather than sex-specific factors for the disease. The vast majority of all AD deaths were to persons aged 65 years and older (53,245, or 98.9%) with a significant portion to those aged 85 and above.

Age-adjusted death rates for the leading causes of death in the United States have been falling for a number of conditions, most notably for diseases of the heart and cerebrovascular disease.[26] The trend for mortality due to AD, however, has been one of rapid increase since 1979. While this trend may reflect changes in the underlying risk of becoming affected by AD, other contributing factors should be noted, including improvements in diagnosis (i.e., the development and wide-spread implementation of diagnostic criteria); an increase in awareness of the condition by physicians, coroners, or funeral directors (who determine the underlying cause of death for the death certificate); and in formal acceptance of the term "Alzheimer's Disease." A particularly large increase in 1999 was likely the result of the adoption of the 10th Revision of the International Classification of Diseases (ICD-10) by the U.S. National Center for Health Statistics (NCHS) for that year, which led to more accurate identification of AD as a true cause of death compared to some other designated cause (e.g., pneumonia, heart attack, or general dementia).[27]

Public and Private Funding for AD Research

Federal

Funding for Alzheimer's research has been a growing priority for NIH since the mid-1980s, and has more than doubled since 1997, keeping pace with the budget for the NIA (**Figure 2**). However, the increase has been relatively modest compared to the budget for all health research, with federal spending for AD comprising 1.23% of the total NIH budget in 1987, growing to 2.44% in 2004. In 2004, NIH spent an estimated $680 million on AD research.[28] For 2005, Congress appropriated $1.06 billion to the NIA for aging-related research. The government current funds over 100 new or ongoing research studies on many topics, including the identification of risk

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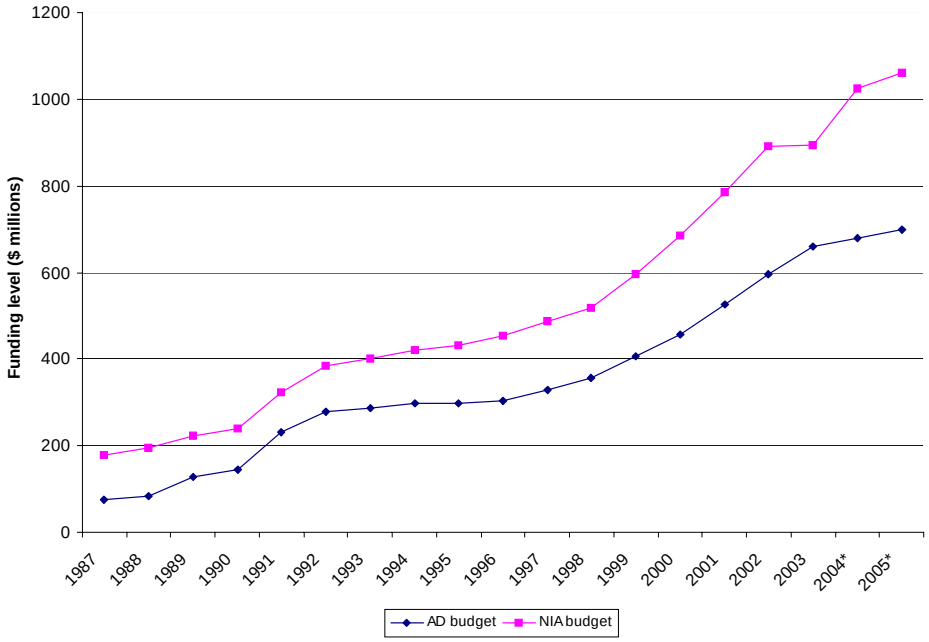
[26] The figures for age-specific and age-adjusted death rates differ slightly. The latter highlights cause-specific mortality trends after adjusting crude rates to eliminate the effect of differences in population composition with respect to age and other variables.

[27] Cause of death data from death certificates are the most widely available, timely, and geographically comparable data on health available for the United States, but their reliability and accuracy are dependent upon the ability of the physician or coroner to make the proper diagnosis and the care with which he records this information on the death certificate. NCHS See also D.C. Ewbank, "Deaths Attributable to Alzheimer's Disease in the United States," *American Journal of Public Health*, Jan. 1999.

[28] U.S. Department of Health and Human Services. Office of the Assistant Secretary for Budget, Technology and Finance, "Alzheimer's Disease," *FY2005 Moyer Material*, Feb. 5, 2004.

factors and new early diagnostic markers for treating AD.[29] While there has been dramatic progress in understanding the disease process, researchers are still searching for more effective means for earlier diagnosis, more effective treatments and preventive strategies, as well as efficient mechanisms to transfer the fruits of research into beneficial services for patients.

Figure 2. NIH Funding (All Agencies) for AD Compared to Total Budget of the NIA, 1987-2004



Source: AD funding, Alzheimer's Disease Funding: "NIH Budget Office," Oct. 5, 2004. See also [http://www.nih.gov/news/fundingresearchareas.html], accessed July 18, 2005. NIA total budget, see [http://www.nih.gov/about/almanac/appropriations/index.htm], accessed July 18, 2005.

Note: Data for 1987-2003 are actual figures; data for 2004 and 2005 are estimates.

Private

Clinical trials evaluating the safety and effectiveness of new diagnostic methods, drugs or other treatments are expensive. Large scale trials of new medical products can cost $10-$30 million.[30] It is difficult to determine the magnitude of private industry investments in AD research, and to determine what clinical trials are

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[29] The exact number depends on whether the search includes only Alzheimer's (as opposed to broader dementia), the type of research supported (human studies, clinical trials, animal models), and other factors. For a list and summary of current clinical trials, see the ClinicalTrials.gov database at [http://www.clinicaltrials.gov].

[30] Alzheimer's Association, Additional Resources Needed to Speed Progress on Treating and *Preventing Alzheimer's Disease*, 2004. Also Alzheimer's Association, personal communication, Apr. 26, 2005.

conducted in the private sector that are not registered with the federal government. The Alzheimer's Association is the largest private funder of AD research, investing over $165 million in 1,300 projects over the past 10 years, including $15.8 million for 71 projects in 2004 alone.[31] The Alzheimer's Association estimates that additional funding is needed in the following areas:

- $50 million for clinical trials;
- $60 million for research to understand risk factors, including $10 million to support the Genetics Initiative sponsored by NIA, and $50 million to examine the relative influence of environmental risk factors;
- $30 million for identifying early markers of disease, including $10 million to support the neuroimaging initiative sponsored by NIA, and $20 million to support community-based epidemiologic studies;
- $60 million for basic science research to increase the number of studies funded from 15% of proposals submitted to NIA to 25% of proposals.

Challenges to the Health Care System

The number of affected persons, the complexity, and the chronic and long-term nature of AD will present unique challenges to the U.S. health care system in the coming decades. The failure of physicians — particularly those in primary care where patients initially seek services — and family members to recognize symptoms of dementia in the early stages, is a major barrier to appropriate care for many AD patients.[32] One study found that general practitioners only identified 3.2% of patients with mild cognitive impairment and 23.5% of patients with moderate to severe dementia.[33] A related medical concern is that while remedies may reduce the incidence (i.e., number of new cases each year) of disease,[34] earlier diagnosis and improved treatments increases the prevalence — or proportion of persons living with AD out of the total population, while not influencing the incidence. According to the Alliance for Aging Research, the United States will fall short of the 36,000 specialists[35] needed by 2030 to meet the medical needs of the aging population.

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[31] Alzheimer's Association at [http://www.alz.org/research/].

[32] Jeffrey L. Cummings, "Alzheimer's Disease," *New England Journal of Medicine*, vol. 351, July 1, 2004, pp. 56-67 (Hereafter cited as Cummings, "Alzheimer's Disease.")

[33] C.M. Callahan, H.C. Hendrie, and W.M. Tierney, "Documentation and Evaluation of Cognitive Impairment in Elderly Primary Care Patients," *Annals of Internal Medicine*, vol. 122 (1995), pp. 422-429.

[34] J.C.S. Breitner, "The End of Alzheimer's Disease?" *International Journal of Geriatric Psychiatry*, vol. 14 (1999), pp. 577-586.

[35] Alliance for Aging Research, "Ten Reasons Why America Is Not Ready for the Coming (continued...)

Even if better biological or genetic markers are developed to improve diagnosis, patients will still need evaluation and testing to determine onset of dementia, prognosis, progression, residual function and hopefully, response to therapy. Identification of earlier markers of AD offers the opportunity to begin preventive treatments to slow the progression of disease, giving patients more time with their families to plan the course of their care and make other life decisions. Additional markers may act to monitor the effectiveness of therapy. Identification of such markers has been a priority for the NIH.[36]

While not a cure, delaying the onset of disease or the time to progression to severe disease still has benefits. The Alzheimer's Association indicated that breakthroughs in medical research could result in nearly a 45% drop in the number of cases (from 6.5 million to 3.6 million), potentially saving up to $149 billion in annual Medicare and Medicaid costs by 2025.[37] A recent study showed that using the newly approved drug, memantine, alone could slow cognitive decline enough to reduce the need for caregiving to 45.8 hours per month,[38] with the potential for better outcomes when combined with other interventions. Likewise, treatment with an established drug (donepezil), may slow progression sufficiently to delay nursing home care for an average of 30 months.[39] While use of the drug would increase treatment costs perhaps as much as four-fold, it may substantially reduce a patient's overall medical costs — in one study, total annual costs were reduced by $3,891 for patients receiving donepezil.[40]

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[35] (...continued)
Age Boom," 2002, available at [http://www.agingresearch.org/bookshelf.cfm].

[36] Testimony of NIA Director Richard Hodes, in U.S. Congress, Senate Committee on Health, Education, Labor and Pensions, Subcommittee on Aging, *Breakthroughs in Alzheimer's Disease: News You Can Use*, hearing, 108th Congress, 2nd sess. May 11, 2004, [http://help.senate.gov/testimony/t95_tes.html].

[37] Report of the Lewin Group to the Alzheimer's Association, "Saving Lives Saving Money: Dividends for Americans Investing In Alzheimer Research," June 23, 2004, pp. 1-7, at [http://www.alz.org/Resources/FactSheets/Lewin_FullReport1.pdf]. This report is subject to a number of important assumptions regarding the prevalence of disease, the rate of technological advancement, and the projected costs of care. These assumptions may be in part, a reason why the costs at baseline are higher (estimated at $189 billion in total Medicare spending in 2015) compared to those cited earlier in this report (total Medicare costs for Alzheimer's were $49.3 billion in 2010). The costs cited earlier in this report were from an earlier report by the Lewin Group (2001).

[38] B. Reisberg, et al., "Memantine in Moderate-to-Severe Alzheimer's Disease," *The New England Journal of Medicine*, vol. 348, no. 14 (2003), pp. 1333-1341.

[39] George Provenzano, et al., "Delays in Nursing Home Placement for Patients with Alzheimer's Disease Associated with Donepezil May Have Health Care Cost Saving Implications," *Value in Health* vol. 4, no. 2 (2001), p. 158.

[40] J.W. Hill, et al., "The Effect of Donepezil Therapy on Health Costs in a Managed Care Plan," *Managed Care Interface*. Mar. 2002, pp. 63-70.

Biomedical Aspects of Alzheimer's Disease

In the absence of the disease, the human brain often can function well into the tenth decade of life.[41] In 1906, Dr. Alois Alzheimer, a German doctor, noticed changes in the brain tissue of a woman who had died of an unusual mental illness. The amyloid plaques and neurofibrillary tangles that he discovered are now considered hallmarks of AD.[42] Until the 1970s, AD was considered a rare disorder, with only a small group of pioneers conducting research on the disease.[43]

The biomedical aspects of Alzheimer's Disease are considered in the next three sections. The *first* section reviews the clinical symptoms of the disease and the biology of AD progression. Though the precise cause of AD is still illusive, much knowledge has been gained through basic research in the understanding of the physical signs and progression of the disease. This section will review major initiatives in basic and clinical research.[44] As knowledge is gained about the process of disease development, treatments can be designed to block or otherwise alter that progression. For clarity, a discussion of current treatments follows the description of the biological factors that they are designed to alter. None of the current treatments provide a definitive or effective cure for AD, though a few may act to slow the progression of cognitive decline.

In the next section ("Diagnosis"), an overview of current and promising means of diagnosing AD based on the clinical signs and symptoms of the disease is presented, along with a discussion of current treatments that target a risk factor and aim to reduce the severity of symptoms and delay cognitive decline.

Finally, the third section will describe the latest research into the newest potential treatments. Together these sections provide an overview of how research dollars are being spent in various basic, clinical and behavioral research settings to determine and affect cause, to prevent or reduce symptoms, and to reverse damage accumulated during disease progression.

The Biology of Alzheimer's Disease

Clinical Signs and Symptoms. AD is a progressive neurodegenerative condition, and a common form of dementia in the elderly. The disease process

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[41] United States Department of Health and Human Services, National Institutes of Health (NIH), National Institute on Aging (NIA), *Alzheimer's Disease: Unraveling the Mystery*, 2002 (Hereafter cited as *DHHS/NIH/NIA, Alzheimer's Disease: Unraveling the Mystery*.)

[42] NIH *Senior Health, Alzheimer's Disease*, Nov. 23, 2003, at [http://nihseniorhealth.gov/alzheimersdisease/defined/04.html].

[43] DHHS/NIH/NIA, *Alzheimer's Disease: Unraveling the Mystery*.

[44] Basic research often uses animal or cell culture models to answer a specific research question. In contrast, clinical (or applied) research involves investigation of a specific intervention in human beings.

usually begins with mild cognitive impairment (MCI),[45] and loss of instrumental activities of daily living (IADLs), such as check writing or use of public transportation. Patients may present with confusion, poor judgement, language disturbances, agitation, and hallucinations.[46] Depression is common in early disease. As the disease progresses, patients experience difficulties in basic activities of daily living (ADLs), such as eating, grooming, bathing, or using the toilet.[47] In addition to the loss of physical abilities, mood changes and apathy occur throughout the course of the illness. During the middle and later phases, psychosis and agitation become commonplace.[48] The disease can last from 8-10 years, with a range of 1-25 years. Death typically results from general inanition (i.e., exhaustion due to malnutrition), malnutrition, and pneumonia.[49] Early onset AD is characterized by appearance of symptoms before age 65, usually between the ages of 40 and 50; however, onset can range from the 30s to early 60s. Late onset AD is characterized by the appearance of symptoms at age 65 or older.

Studies of AD are difficult, because exact diagnosis is not possible without an examination of brain tissue which is not available until after the patient has died. As a result, the precise cause of AD remains unknown, but is postulated to be both multifactorial (meaning that there are multiple causes) and polygeneic (i.e., multiple genes[50] are involved). Much of what is known has been derived from animal models, such as transgenic (i.e., genetically modified) mice.

AD results from a disruption of normal brain structure and function. **Table 4** summarizes the frequency of different types of AD. One thing that contributes to the disruption is a buildup of protein called beta-amyloid. The majority of the cases occur sporadically, with no familial influence or obvious exposure. However,

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[45] MCI is different from both AD and normal age-related memory change. People with MCI have ongoing memory problems but do not have other losses like confusion, attention problems, and difficulty with language. See the Alzheimer's Disease Education and Referral Center (ADEAR) at [http://www.alzheimers.org/generalinfo.htm].

[46] Thomas D. Bird, *Alzheimer Disease Overview*, Sept. 12, 2003. Available at [http://www.genetests.org] (Hereafter cited as Bird, *Alzheimer Disease Overview*).

[47] D. Galasko, et al., "An inventory to Assess Activities of Daily Living for Clinical Trials in Alzheimer's Disease: the Alzheimer's Disease Cooperative Study," *Alzheimer Disease and Associated Disorders*, vol. 11, suppl. 2 (1997), pp. S33-S39.

[48] M.S. Mega, J.L. Cummings, T. Fiorello, and J. Gornbein, "The Spectrum of Behavioral Changes in Alzheimer's Disease," *Neurology*, vol. 46 (1996), pp. 130-135.

[49] American Psychiatric Association (APA), *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed. (Washington, D.C.: APA, 1994), pp. 139-145.

[50] Genes are pieces of DNA which encode the biochemical sequence that can be translated into proteins. Each person usually inherits two copies of a gene (one from their mother, one from their father). The different forms of a gene are called alleles. Differences in the gene sequences that differentiate the alleles can result in different versions — or isoforms — of a protein. CRS Report RL32478, *Genetic Testing: Scientific Background and Nondiscrimination Legislation*, by Michele Schoonmaker and Erin Williams, includes a brief discussion of the relationship between genes and proteins.

approximately 25% of patients have relatives with AD (i.e., the disease 'runs in their families'). Clinically, familial cases look the same as sporadic cases.

The gene that codes for the amyloid protein is found on chromosome 21. 'Normal' individuals have two copies of chromosome 21, and therefore two copies of the gene for amyloid protein. Down syndrome patients have three copies of chromosome 21 (and therefore three copies of the gene for amyloid protein). Because Down syndrome patients have three copies of chromosome 21, a rare few of AD cases (less than 1%) can be associated with Down syndrome.

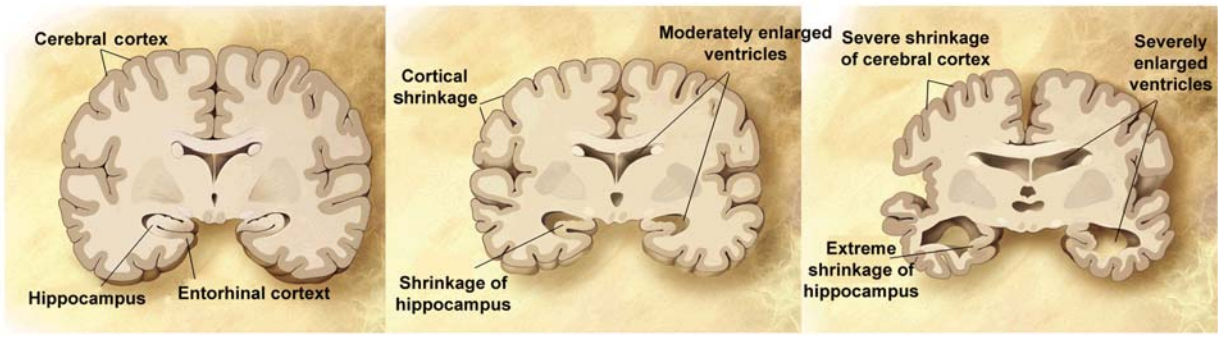
Table 4. Types of AD

Type of AD	Frequency
Sporadic (e.g., no family history)	75%
Familial	25%
Late onset	15-25%
Early onset	< 2%
Chromosomal (e.g., trisomy 21)	< 1%

Source: Bird, *Alzheimer's Disease Overview.*

Physiological Changes and Pharmaceutical Targets. The damage to the AD brain is selective and concentrated in the areas that are concerned with memory, language, reasoning and judgement. The most striking damage is generalized atrophy (i.e., shrinking) of the brain[51] and enlargement of cavities (known as ventricles) which occurs when nerve cells begin to die (**Figure 3**).

Figure 3. Physical Changes in Brain with Alzheimer's Disease



Source: Alzheimer's Disease Education & Referral Center (ADEAR), "Alzheimer's Disease: Unraveling the Mystery," at [http://www.alzheimers.org/unraveling/07.htm].

[51] The University of California Los Angeles (UCLA) Laboratory of NeuroImaging (LONI) website hosts a computer animation which demonstrates changes in the gross structure of a normal human brain as it is transformed by AD. See "Elderly Normal to Elderly Alzheimer's Disease Warp" at [http://www.loni.ucla.edu/SVG/Animations/Disease.html].

Though still unproven, the "amyloid hypothesis" is the most well-supported theory of how AD develops. In this theory, the cascade of biological events leading to AD are (1) beta-amyloid accumulates in the brain in the form of plaques; (2) neurofibrillary tangles form, (3) inflammation occurs around the plaques and tangles and finally, (4) cell death is initiated. At some point in the cascade, the neurons (i.e., nerve cells) become dysfunctional in their ability to communicate with one another. Scientists do not always agree which of these steps are causal or which are effects of disease.

Established treatments have focused on multiple stages in the AD disease process. Some target the process of plaque formation. Other therapies attempt to inhibit the inflammatory response that occurs in response to the plaques, or attempt to improve function by replenishing neurotransmitters, growth factors or hormonal therapies.[52] Each of the steps in the disease process will be discussed below along with the corresponding opportunities for therapeutic interventions.

Amyloid Protein. On a microscopic level, the AD brain is characterized by the accumulation of amyloid plaques and neurofibrillary tangles. A large protein called amyloid precursor protein (APP) is broken down (i.e., cleaved) into smaller amyloid proteins, called beta-amyloid-40 and beta-amyloid-42. The number signifies how many amino acids (i.e., the chemical building blocks of proteins) are in each. Of these cleavage products, beta-amyloid-42 is more likely to be in plaques and be toxic to cells. APP and its cleavage products may occur in normal cells and cerebrospinal fluid,[53] but their function is not known.[54]

In Alzheimer's, the beta-amyloid product builds up around nerve cells in a bad form (known as a beta-pleated sheet) and eventually forms the characteristic plaque (**Figure 4**). The mechanisms of how the beta-amyloid protein is allowed to accumulate are still unclear. In some cases, mutations in the APP gene (i.e., the genetic material that is the blueprint for the protein) or abnormal processing of the APP by enzymes called secretases may result in the overproduction of beta-amyloid. In other instances, the accumulation may be mediated by another unknown factor, or may be due to the brain's inability to clear toxic forms of the protein.[55]

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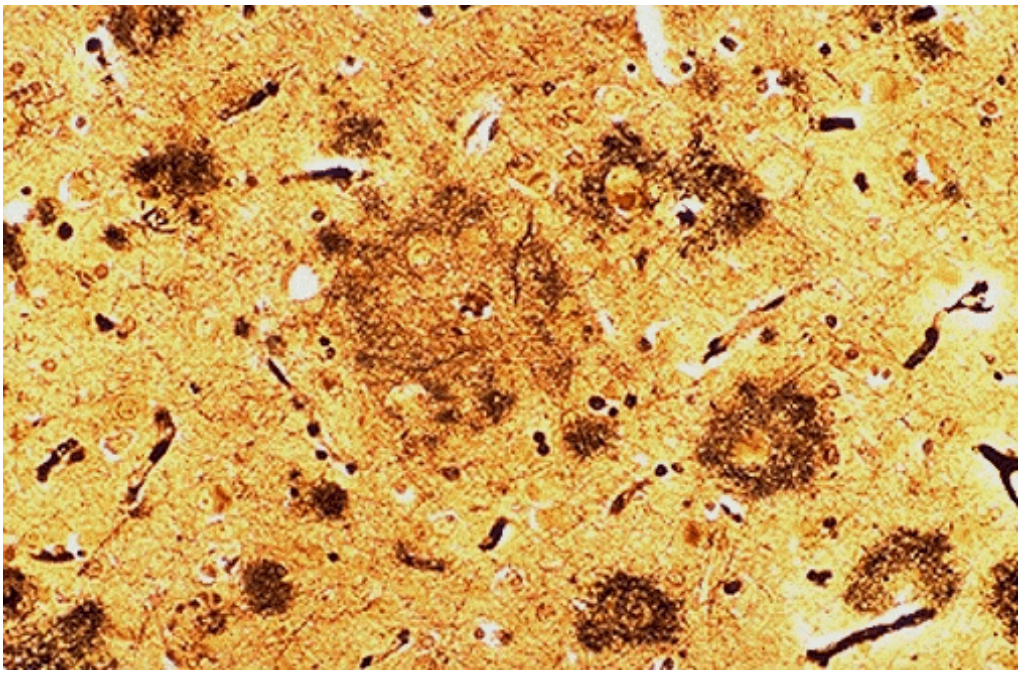
[52] DHHS, *Mental Health: A Report of the Surgeon General*, Chapter 5: Older Adults and Mental Health, Section 4: Alzheimer's Disease at [http://www.surgeongeneral.gov/library/mentalhealth/chapter5/sec4.html].

[53] Dennis J. Selkoe, "Alzheimer's Disease: Mechanistic Understanding Predicts Novel Therapies," *Annals of Internal Medicine*, vol. 140, 2004, pp. 627-38 (Hereafter cited as Selkoe, *Alzheimer's Disease: Mechanistic Understanding*.)

[54] A. Kamal, et al., "Kinesin-Mediated Axonal Transport of a Membrane Compartment Containing Beta-secretase and Presenilin-1 Requires APP," *Nature*, vol. 414, 2001, pp. 643-648.

[55] R.N. Rosenberg, "The Molecular and Genetic Basis of AD: The End of the Beginning," *Neurology*, vol. 54, 2000, pp. 2045-2054. (Hereafter cited as Rosenberg, *The Molecular and Genetic Basis* of AD.)

Figure 4. Microscopic Image of the AD Brain



Source: CNS Pathology at [http://www-medlib.med.utah.edu/WebPath/CNSHTML/CNS090.html], accessed May 26, 2005.

Notes: The large dark spots are the amyloid plaques and the smaller, darker, irregular shaped structures are the tangles.

The presence of plaques is not limited to AD. In fact, in normal aging there is some neuronal loss, and some healthy individuals even develop a few scattered plaques and tangles, making an early diagnosis of AD difficult.

To date, there are no therapies available to effectively reduce or eliminate beta-amyloid from the brain.[56] Researchers are investigating strategies to inhibit secretase (and therefore inhibit beta-amyloid synthesis) as potential therapies.[57] One vaccine clinical trial was stopped in 2003 when 6% of the patients experienced serious side effects.[58]

Neurofibrillary Tangles. Neurofibrillary tangles are the dense, irregularly shaped structures in **Figure 4**. They are made of microtubules. The microtubules are the structures that neurons use to carry substances within the body of the cell and to its many projections, called dendrites. These microtubules are made up of proteins called tau proteins. In AD, a change in the chemical make up of the tau proteins

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[56] Cummings, "Alzheimer's Disease,", pp. 56-57.

[57] Rosenberg, *The Molecular and Genetic Basis of AD.*

[58] Jean-Marc Orgogozo, et al., "Subacute Meningoencephalitis in a Subset of Patients with AD After Abeta42 Immunization," *Neurology*, vol. 61, 2003, pp. 46-54, in Cummings, "Alzheimer's Disease."

causes them to rearrange and weaken the support system for the nerve cell. The cell then changes shape and loses its ability to communicate with other nerve cells. The cell eventually dies, but the tangles remain. Tangles can occur in the absence of beta-amyloid plaques, and do so in other diseases such as frontotemporal dementia.[59]

Inflammatory Response. As plaques and tangles form, the brain launches a localized inflammatory response against the dying nerve cells and abnormal proteins. Studies show that signs of inflammation occur from early to late disease. These signs include the association of inflammatory proteins with plaques, and the accumulation and activation of microglial cells[60] around the plaques. While inflammation is a normal response to injury or disease, chronic inflammation can be harmful to tissues.

Some researchers suggest that the inflammatory proteins may be involved in the regulation of APP synthesis and actually aggravate the disease. In this model, the APP is made and cleaved into the beta-amyloid protein. The toxic form of beta-amyloid then activates microglial cells to produce inflammatory proteins. The inflammatory proteins then stimulate production of more APP, which then is converted to beta-amyloid, and so on, eventually leading to the build-up of beta-amyloid into a plaque.[61]

Anti-Inflammatory Medications. Regardless of the mechanism by which inflammation acts (i.e., whether chronic inflammation causes general damage to brain tissue or the inflammatory proteins are somehow more specifically involved in plaque formation), researchers are investigating whether non-steroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen, can slow the disease progression as suggested by epidemiologic studies. Despite the epidemiologic evidence, negative results have been reported for trials of diclofenac, rofecoxib (Vioxx),[62] and naproxen (e.g., Aleve, Naprosyn).[63] As a result insufficient evidence exists to support long-term treatment with NSAIDs. Some researchers argue that comparisons between different NSAIDs are difficult because they have different mechanisms of action. Current studies are evaluating the value of new NSAIDs (such as celecoxib, human recombinant interferon-alpha, and cyclophosphamine) in preventing AD.

Neurotransmitters. A neurotransmitter is a chemical made by a nerve cell. It is used to transmit signals from one neuron to either another neuron or other cell (such as a skeletal muscle cell or heart muscle cell). When a neuron is stimulated, it releases a neurotransmitter from the ends of the dendrites (**Figure 5**). The

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[59] Selkoe, *Alzheimer's Disease: Mechanistic Understanding*.

[60] Microglial cells are immune cells that engulf and clear dead cells and debris in the brain.

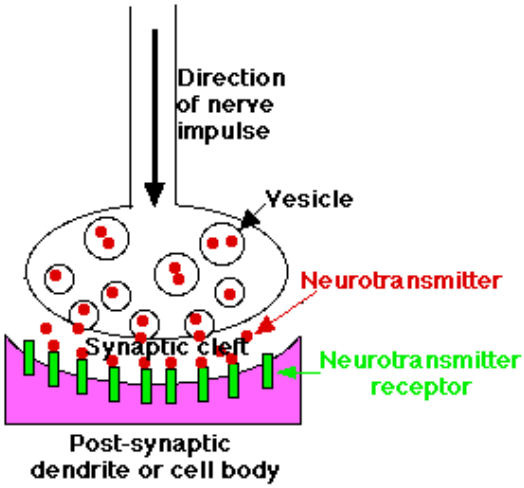
[61] J. M. Hoozemans, et al., "Immunological Aspects of Alzheimer's Disease," *BioDrugs*, vol. 15, no. 5 (2001), pp. 325-337.

[62] Vioxx was recently removed from the market due to excessive adverse cardiac events associated with its use for rheumatoid arthritis. Public health advisories have been issued for other NSAIDs, including some sold over-the-counter, such as ibuprofen. See [http://www.pueblo.gsa.gov/nsaid.htm]. Accessed Apr. 26, 2005.

[63] Cummings, "Alzheimer's Disease."

neurotransmitter rapidly travels the small gap (called the synapse) between the first neuron (called the pre-synaptic neuron), and binds to a special receptor on the dendrite of a neighboring neuron (post-synaptic). The binding of the neurotransmitter to its receptor elicits an electrochemical response (called depolarization) in the second neuron, which stimulates it to release a neurotransmitter to stimulate the next neuron. The movement of electrochemical signals and the release of neurotransmitters occur in one direction along a nerve, and are what allows neurons to communicate with each other (**Figure 5**).

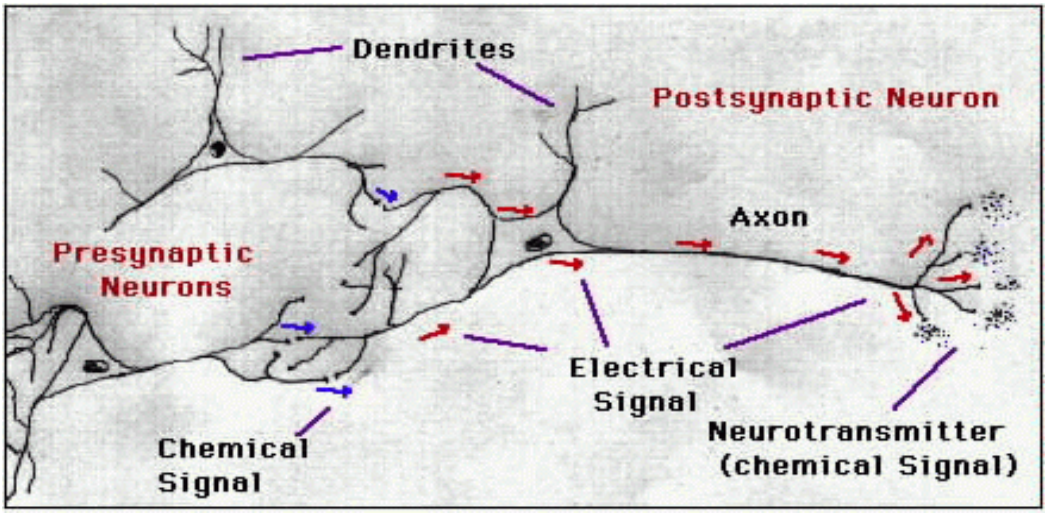
Figure 5. Neurotransmitter Function



Source: [http://users.rcn.com/jkimball.ma.ultranet/BiologyPages/S/Synapses.html].

When the signal has been transmitted, the neurotransmitter must be removed from the synapse. For almost all neurotransmitters, removal occurs by a process called reuptake. In reuptake, the neurotransmitter is actively re-absorbed by the presynaptic neuron.

Figure 6. Movement of a Signal Between Neurons



Source: Instituto de Fisiología Celular, *The Neuron* at [http://www.ifisiol.unam.mx/ Brain/neuron. htm].

Neurotransmitters can be small molecules (such as acetylcholine (ACH), dopamine, norepinephrine, serotonin, histamine, and epinephrine), amino acids (such as gamma-aminobutyric acid (GABA), glycine, glutamate, and aspartate), peptides (such as insulin, neuropeptide Y, or somatostatin among others) or even soluble gases (carbon monoxide or nitric oxide).

Acetylcholine. The cholinergic system consists of all of the neurons that use acetylcholine (ACH) as their neurotransmitter. ACH has been shown to have a central role in information processing, memory, and learning. It is made from other chemicals by an enzyme called choline acetyltransferase. The degenerative progression in AD has been associated with deficits in the cholinergic system. The deficits could be due to the death of cholinergic neurons (i.e, neurons that make or use ACH) which reduces the amount of ACH that is available.

ACH can be released into the synapse by two different receptors, called the muscarinic and nicotinic receptors.[64] These receptors can also bind other molecules. Depending on the molecule encountered, the receptor will signal the increased or decreased release of ACH into the synapse. When the signal has been transmitted, the neurotransmitter must be deactivated. Unlike most other neurotransmitters which are deactivated by a reuptake mechanism, ACH is broken down into inactive fragments by an enzyme called acetylcholinesterase.

Glutamate. Glutamate is a neurotransmitter that binds to another kind of receptor, called the NMDA (N-methyl-D-aspartate) receptor. When glutamate binds to the NMDA receptor, it triggers calcium to flow into the neuron. Calcium flow into and out of the neuron is important for depolarization to occur. For the brain to store information and function properly, there must be a balance between the levels of glutamate and calcium. If there is not enough glutamate to bind NMDA receptors, calcium cannot enter the cell and information cannot be stored. On the other hand, if too much glutamate is available, too much calcium enters the neuron, and the neuron may die.[65]

Treatment with Neurotransmitter Modulators. The ACH system has long been the target for therapeutic intervention. Drugs have sought to increase the amount of ACH that is available by stimulating its production, by inhibiting the enzymes that break it down, or by affecting the receptors to which ACH binds. Four

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[64] Muscarinic receptors are found between the junction of nerve cells and cardiac or smooth muscles, and between nerve cells that control sympathetic nervous function. Sympathetic nervous function is responsible for the body's response to stress. Stimulation of sympathetic nerves causes the heartbeat to increase, blood pressure to rise, and digestive movement to slow. Nicotinic receptors are found at the junction between nerve cells and skeletal muscle, and between neurons that control parasympathetic nervous function. Parasympathetic nervous function is responsible for returning the body to normal after a stressful encounter (e.g., lowers blood pressure, lowers heart beat, increase digestive movement).

[65] *Namanda (memantine) Information for Consumers*, available at [http://www.namenda.com/treating/how.asp].

drugs[66] that act to influence neurotransmitter function have been approved by the Food and Drug Administration (FDA) for the treatment of AD (**Table 5**). Donepezil (Aricept™), rivastigmine (Exelon™) and galantamine (Reminyl™) inhibit acetylcholinesterase, leaving more acetylcholine in the synapse to foster communication between neurons. In addition, galantamine actually stimulates the nicotinic receptors of the nerve cells to make more acetylcholine.

The most frequent side effects of cholinesterase inhibitors are nausea and vomiting, diarrhea, stomach cramps and headaches, dizziness, fatigue, insomnia and loss of appetite.[67] Evidence suggests that treatment with cholinesterase inhibitors may delay the onset of AD symptoms by 6-24 months.[68] While cholinesterase inhibitors have demonstrated effectiveness for improving cognition and/or attention associated with mild to moderate disease, the effects still are not clear in later stages.[69] There have been no direct comparisons of these drugs, and the main differences in utilization may be due to the ease of administration and side effect profiles rather than their efficacy.[70]

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[66] A fifth drug, tacrine, was one of the first approved by the Food and Drug Administration (FDA), but now is rarely used due to increased adverse side effects in the liver.

[67] Alzheimer's Society, "After the Diagnosis: Drug Treatments for Alzheimer's Disease - Aricept, Exelon, Reminyl and Ebixa," Nov. 2000. Available at [http://www.alzheimers.org.uk/After_diagnosis/Treatments/info_drugs.htm].

[68] E. Giacobini, "Cholinesterase Inhibitor Therapy Stabilizes Symptoms of Alzheimer Disease," *Alzheimer Disease and Associated Disorders*, vol. 14, 2000, pp. S3-S10.

[69] Most trials have only measured the effects of the cholinesterase inhibitor for 6-12 months, and one, using extrapolated data for the placebo group, suggested that patients continued to benefit from therapy for two-three years. See Cummings, *Alzheimer's Disease*.

[70] R.S. Doody, et al., "Practice Parameter: Management of Dementia, Report of the Quality Standards Subcommittee of the American Academy of Neurology," *Neurology*, vol. 56, 2001, pp. 1154-1166. (Hereafter cited as Doody et al., *Practice Parameter*).

Table 5. FDA Approved Anti-Dementia Drugs for Treatment of AD

Common (trade) name	Date of approval and manufacturer	Approved indications	Mechanism of action
Donepezil (Aricept)	11/25/1996; Eisai and Pfizer	For treatment of mild to moderate dementia of Alzheimer's type.	Inhibits Acetylcholin-esterase
Rivastigmine (Exelon)	4/21/2000; Novartis	For treatment of mild to moderate dementia of Alzheimer's type.	Inhibits Acetylcholin-esterase
Galantamine (Reminyl)	2/28/2001; Shire, Inc.	For treatment of mild to moderate dementia of Alzheimer's type.	Inhibits Acetylcholin-esterase; stimulates acetylcholine production (nicotinic receptors)
Memantine (Namenda, aka Ebixa in UK)	10/27/2003; Merz	For the treatment of moderate to severe dementia of the Alzheimer's type	Blocks glutamate binding to NMDA-receptors

Source: CRS compilation.

A recently approved drug, memantine (Namenda™) helps to regulate the activity of glutamate by binding to the NMDA receptor. While memantine is mildly effective in stabilizing or improving cognition at the middle to later stages of AD, there is no evidence at this time to show that it slows or prevents neurodegeneration.[71] Memantine therapy may be combined with other therapies like vitamin E or a cholinesterase inhibitor, since they have a different mechanism of action. Combination therapy may result in some cognitive and behavioral improvement compared to placebo. Like other drugs, the effects of memantine, however, are temporary (i.e., does not stop, cure, or reverse the disease).[72]

Though still at a very early stage, pharmacogenomic data may eventually prove useful in identifying which patients are likely to respond to different medications, and which may experience serious adverse events. For example, FDA approved labeling

[71] Namanda (memantine) FDA-approved product labeling, available at [http://www.fda.gov/cder/foi/label/2003/021487lbl.pdf].

[72] P.N. Tariot, et al., "Memantine Treatment in Patients with Moderate to Severe Alzheimer Disease Already Receiving Donepezil: A Randomized Controlled Trial," *Journal of the American Medical Association*, vol. 291(2004), pp. 317-324.

for Reminyl states that 7% of patients treated may have a genetic variation which would slow the rate that the drug is cleared from their bodies (i.e., poor metabolizer), potentially leading to toxic build-ups.[73] The implication of this information is that these patients may receive either a lower than recommended dosage or a different drug to minimize their risks of adverse events.

Apoliprotein E. Apolipoprotein E (ApoE) is a well characterized lipoprotein[74] that is normally found in plasma and cerebrospinal fluid. ApoE is involved in lipid metabolism. It is particularly important for bringing cholesterol into neurons during brain development and in response to neuronal injury. ApoE normally recycles cholesterol from dying neurons by forming a complex with it and other lipoproteins inside the dying cell. The complex is then released into circulation where it can bind with a receptor site (the low density lipoprotein receptor: LPR) on a healthy cell and become internalized. The cholesterol is released and used to make new neuronal dendrites or in re-building synapses.[75]

The LPRs can also interact with APP, beta-amyloid, and other proteins involved in lipid metabolism (such as alpha-2 macroglobulin), and may mediate the clearance of ApoE/beta-amyloid or protein/beta-amyloid complexes from the brain.[76] LPR is also found in the beta-amyloid plaque.[77]

There are three main forms of the ApoE lipoprotein: ApoE2, E3 and E4 which result from variation in the ApoE gene locus. In 1993, research demonstrated that the ApoE4 allele (i.e., form of the gene) was more frequent in AD patients compared to those without AD, particularly in cases with an early age of onset.[78] In AD, ApoE4 may produce increased risk through abnormal cholesterol metabolism.[79] It has been hypothesized that ApoE4 may be involved with the degradation of amyloid or may disrupt the removal of beta-amyloid from brain tissue leading to accelerated buildup

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[73] Reminyl (galantamine) FDA-approved labeling, available at [http://www.fda.gov/cder/foi/label/2002/21224s3lbl.pdf].

[74] A lipoprotein is a combination of a fat and a protein that usually carries other lipids — such as cholesterol — through the blood.

[75] Judes Poirier, "ApolipoproteinE: A Pharmacogenetic Target for the Treatment of Alzheimer's Disease," *Molecular Diagnosis*, vol. 4, no. 4 (1999), pp. 335-341.

[76] Rosenberg, *The Molecular and Genetic Basis of AD*.

[77] Bradley T. Hyman, Dudley Strickland, and William Rebeck, "The Role of Low Density Lipoptotein Receptor Related Protein (LPR) in beta-Amyloid Metabolism and Alzheimer's Disease," *Archives of Neurology*, vol. 57, 2000, pp. 646-650.

[78] See references 9-11 in Poirier, "ApolipoproteinE: A Pharmacogenetic Target for the Treatment of Alzheimer's Disease," *Molecular Diagnosis*, vol. 4, no. 4 (1999).

[79] Rosenberg, *The Molecular and Genetic Basis of AD*.

of the toxic protein.[80] ApoE4 has been associated with other diseases, such as HIV-associated dementia,[81] cerebral palsy,[82] and cardiovascular disease.[83]

Statins. (Cholesterol Lowering Drugs). Because cholesterol metabolism may be linked to the generation of the beta-amyloid plaques, researchers have suggested that cholesterol-lowering drugs (statins[84]) may be beneficial in reducing the accumulation of beta-amyloid.[85] However, because studies to date have been relatively small, professional groups do not recommend that a patient take statins solely to combat Alzheimer's.[86] One study investigating the ability of a statin (simvastitin) to slow disease progression in 400 individuals with mild to moderate AD was recruiting patients as of September 2004[87].

Environmental Risk Factors. The majority of AD patients do not have a family history. Even though it has often been speculated that late onset disease results from exposure to an unknown environmental agent on a predisposing genetic background, no environmental agents have been definitively proven to cause AD.[88] Many of the studies linking risk factors to AD are epidemiologic (i.e., population-based); conclusions usually support evidence of an association, but not of causality. Additional research controlling for potential bias or unmeasured risk factors is necessary to separate true associations from spurious ones, and to confirm the epidemiologic findings.[89] Trauma, smoking, and exposure to pesticides may increase

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[80] Peter H. St. George-Hyslop, "Molecular Genetics of Alzheimer's Disease," *Biological Psychiatry*, vol. 47, 2000, pp. 183-199.

[81] E.H. Coder, et al., "HIV-Infected Subjects with the E4 Allele for ApoE Have Excess Dementia and Peripheral Neuropathy," *Nature Medicine*, vol. 10, 1998, pp. 1182-1184.

[82] Erika Meirelles Kalil Pessoa de Barros; Rodrugues, Consuela Junqueira; Pessoa de Barros, Tarcisio; Bevilacqua, and Ruy Geraldo, "Presence of Apolipoprotien E4 Allele in Cerebral Palsy," *Journal of Pediatric Orthopedics*, vol. 20, 2000, pp. 786-789.

[83] F.M. Van Bockxmeer, C.D. Mamotte, F.R. Gibbons, and R.R. Taylor,, "Apoliprotein Epsilon 4 Homozygosity — A Determinant of Restinosis after Coronary Angioplasty," *Atherosclerosis*, vol. 110, 1994, pp. 195-202.

[84] FDA approved statins include Atorvastatin (Lipitor®), Fluvastatin (Lescol®), Lovastatin (Mevacor®), Pravastatin (Pravachol®), Simvastitin (Zocor®), among others, see [http://www.fda.gov/cder/].

[85] Suzana S. Petanceska; S. DeRosa; V. Olm, N Diaz, A. Sharma, T. Thomas-Bryant, K. Duff, M. Pappolla, and L.M. Refolo, "Statin Therapy for Alzheimer's Disease: Will It Work?" *Journal of Molecular Neuroscience*, vol. 19, 2002, pp. 155-161.

[86] Alzheimer's Association, "Facts About Statins and Alzheimer's Disease," Feb. 10, 2003, available at [http://www.alz.org].

[87] See [http://www.clinicaltrials.gov].

[88] Bird, *Alzheimer Disease Overview*.

[89] Steven D. Edland, Susan Slager, and Matthew Farrer, "Genetic Association Studies in Alzheimer's Disease Research: Challenges and Opportunities," *Statistics in Medicine*, vol. 23, 2004, pp. 169-178.

risk of developing AD.[90] Other risk factors are similar to those for heart disease and stroke (i.e., high cholesterol, high blood pressure, diabetes).[91] However, it is unclear if these risks are specific for other types of dementia or for conditions that may co-exist with or accelerate the AD.

On the protective side, higher education, and time spent in physical or mental activities during life have been associated with a lower risk of AD.[92] Though alcoholism has been associated with dementia, a few studies have demonstrated that light to moderate drinking may have a beneficial effect in reducing Alzheimer's risk, possibly related to the antioxidant properties of alcohol or its effect on lipid metabolism.[93] Other studies suggest that dietary folic acid may protect neurons against DNA damage by lowering levels of homocysteine.[94] Folic acid can also cause cholesterol to become oxidized into low-density lipoprotein, which is damaging to the arteries. Low calorie diets may protect against aging in general.[95] To date, none of these potential neuroprotective dietary agents or interventions have been shown to be of benefit for people who already have symptoms.

Infectious agents have also been investigated as having a possible role in sporadic cases of AD. Herpes simplex virus (HSV-1) is a neurotropic infectious agent that has been shown to be a risk factor for AD, potentially predisposing individuals to increased inflammation, plaque and tangle formation. Most (80%-90%) humans have antibodies to HSV-1, indicating that they have been exposed to the virus (mostly in the form of oral cold sores). Many exposures will result in mild or asymptomatic disease. HSV-1 reproduces in the sensory nerves near the site of infection. It can lay dormant in the nervous system. The theory is that HSV-1 reactivation causes neuronal injury which can predispose an individual to AD. No clinical trials have been initiated that would investigate the effectiveness of antiviral treatments, such as acyclovir, in treating AD. A few studies have shown an increased frequency of the ApoE4 allele in patients that test positive for HSV-1, indicating a possible interaction between ApoE and herpes disease recurrence.[96]

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[90] Though nicotine as a treatment (binding to the nicotinic receptors) may offer some benefit, smoking does not seem to reduce risk. See Richard Mayeux, "Epidemiology of "Neurodegeneration," *Annual Reviews of Neuroscience*, vol. 26, 2003, pp. 81-104 (Hereafter cited as Mayeux, *Epidemiology of Neurodegeneration*.)

[91] Monique M. Breteler, "Vascular Risk Factors for Alzheimer's Disease: An Epidemiologic Perspective," *Neurobiology of Aging*, vol. 21, 2000, pp. 153-160.

[92] Mayeux, *Epidemiology of Neurodegeneration*.

[93] Ibid.

[94] Homocysteine is an amino acid that is produced in the body. If allowed to accumulate, it can irritate blood vessels and cause blockage.

[95] Mark P. Mattson, "Gene-Diet Interactions in Brain Aging and Neurodegenerative Disorders," *Annals of Internal Medicine*, vol. 135, 2003, pp. 441-444.

[96] Richard B. Pyles, "The Association of Herpes Simplex Virus and Alzheimer's Disease: A Potential Synthesis of Genetic and Environmental Factors," *Herpes*, vol. 8, 2001, p. 64-68.

Some researchers have postulated links between AD and prion diseases[97] due to similarities in the biochemical mechanisms by which the disease-associated proteins are processed.[98]

A major genetics initiative is now underway, sponsored by NIA in collaboration with the Alzheimer's Association to locate families with two or more affected members. Histories are taken and specimens are banked for genetic testing. The Genetics Initiative seeks to understand the relative influence of genetic and environmental interactions contributing to AD.[99]

Other Potential Interventions to Reduce Risk.

Hormone Therapy. Epidemiologic studies have shown that postmenopausal women who were taking estrogen replacement therapy had a lower incidence of AD. However, to date, randomized trials have not confirmed any benefit. Other hormones — such as progesterone, dehydroepiandrosterone (DHEA), and melatonin have produced similar negative effects.[100] Five trials are currently underway investigating different hormone formulations. Until these trials are concluded, hormone therapy is not recommended solely for treatment of AD.

Vitamins and Dietary Supplements. Free radicals are highly reactive, chemically unstable molecules that interact with cell structures causing damage. The most common free radical in biological systems is the radical form of oxygen. A main theory of aging states that free radical damage occurs constantly within a cell. When the cell can no longer repair the damage caused by free radicals, the cell dies.

Antioxidants are compounds that prevent damage to cells due to free radicals by helping the cell eliminate them. Several studies support the concept that vitamins, particularly vitamin E (an antioxidant) and vitamin C, may delay the onset of symptoms of AD which are thought — in part — to result from oxidative damage.[101] Some physicians recommend high dose vitamin E supplements along with standard

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[97] Prion diseases (also known as transmissible spongiform encephalopathies such as Mad Cow Disease) are rapidly progressive, and uniformly fatal diseases that can affect humans and animals. Cases of the disease are thought be either acquired (sporadic) through infection or may be inherited. Evidence suggests that 'prions' are not viruses, but may be abnormal proteins that, once in the body, have the ability to affect normal organ function.

[98] Frédéric Checler and Bruno Vincent, "Alzheimer's and Prion Diseases: Distinct Pathologies, Common Proteolytic Denominators," *Trends in Neurosciences*, vol. 25, no. 12, Dec. 2002, pp. 616-620.

[99] See [http://www.alzheimers.org/adgeneticsbrochure.pdf].

[100] Brian R. Ott and Norma J. Owens, "Complementary and Alternative Medicines for Alzheimer's Disease," *Journal of Geriatric Psychiatry and Neurology*, vol. 11, 1998, pp. 167-173 (Hereafter cited as Ott and Owens, *Complementary and Alternative Medicines*.)

[101] Cummings, "Alzheimer's Disease."

FDA approved therapy,[102] while others are not convinced.[103] Studies of the potential benefits of other vitamins, such as B_1 and B_{12}, have not been conclusive.[104]

Before 1994, dietary supplements were regulated by the FDA. However, since the Dietary Supplements Health and Education Act of 1994, FDA overview of supplements has been limited to ensuring good manufacturing practices and labeling review. Unlike traditional medicines, FDA does not review or approve the safety and effectiveness of a supplement before they are marketed. Thus, though the manufacturer is responsible for ensuring the safety of dietary supplement products, FDA can take regulatory action if a supplement represents a significant risk of illness or injury to an individual. Labeling for supplements is limited to general statements; manufacturers cannot portray the product as being able to "diagnose, prevent, mitigate, treat, or cure a disease." Both FDA and the Federal Trade Commission (FTC) have jurisdiction over labeling and advertising of dietary supplements.[105]

Herbal remedies are commonly used by patients and their families. Ginkgo Biloba is a herbal remedy that has been used in Europe for treatment of a variety of cerebrovascular conditions. Studies have shown that gingko biloba may have positive effects on cholinergic neurotransmission by increasing the number of muscarinic receptors and the rate of acetylcholine turnover,[106] and may act as an antioxidant.[107] Because ginkgo biloba is comprised of many active ingredients, it is difficult to standardize compounds from different manufacturers for study, and to optimize dosage for a study. Other studies have demonstrated no effect of herbal remedies like ginseng and ginkgo biloba on improving cognition or memory.[108]

Ginseng has been used in Chinese medicine for 5000 years as a treatment for many different conditions, such as fatigue, diabetes, and other disorders of aging. It acts to release adrenocorticotropic hormone, which stimulates nerve growth factor and exerts estrogen-like activity. Animal models have shown that it may stimulate

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[102] Doody et al., *Practice Parameter*. Also see [http://www.alzheimersupport.com/articles/alz3.cfm], accessed Apr. 26, 2005.

[103] Deborah Blacker, *Mild Cognitive Impairment — No Benefit from Vitamin E, Little from Donepezil*, published at [http://content.nejm.org/] Apr. 13, 2005.

[104] Ott and Owens, *Complementary and Alternative Medicines*.

[105] FDA, Center for Food Safety and Applied Nutrition, "Overview of Dietary Supplements," at [http://www.cfsan.fda.gov/~dms/ds-oview.html].

[106] Turan Itil and David Martorano, "Natural Substances in Psychiatry (Ginkogo Biloba in Dementia)," *Psychopharmacological Bulletin*, vol. 31, 1995, pp. 147-158.

[107] M. Zimmermann, et al., "Ginkgo Biloba Extract: from Molecular Mechanisms to the Treatment of Alzheimer's Disease," *Cellular and Molecular Biology*, vol. 48, no. 6, 2002, pp. 613-623.

[108] J. Persson, et al., "The Memory-Enhancing Effects of Ginseng and Ginkgo Biloba in Healthy Volunteers," *Psychopharmacology*, vol. 172, 2004, pp. 430-434.

acetylcholine release, and have some anti-inflammatory effects. Ginseng has not been studied specifically for AD.[109]

Huperzine A is a compound isolated from club moss. The dried herb has long been used as an alternative medicine in China for the treatment of several conditions, including schizophrenia.[110] Huperzine A is a potent inhibitor of aceytlcholinesterase that crosses the blood-brain barrier. Compared to synthetic acetylcholinesterase inhibitors, it may have a longer duration of action and higher therapeutic index. An early clinical trial of huperzine A and AD in China demonstrated positive results,[111] and since has been approved and used clinically in China to relieve symptoms.[112] A trial of 150 patients is currently underway in the United States.

Other compounds have been evaluated for their potential to impact AD progression, including dietary choline (in the form of lecithin, which is an emulsifier found in processed foods) and other chemicals in food. However, well designed clinical studies have failed to show improvements in cognition with these agents.[113]

Other Medications. AD patients also take a number of other drugs in an attempt to reduce symptoms, including tranquillizers, antidepressants, mood stabilizers, anti-anxiety drugs, hypnotics and anti-convulsants.[114] The use of these drugs primarily occurs "off-label," meaning that few of these drugs have been approved by FDA for use in patients with dementia or AD.[115]

Nonpharmacologic Intervention. Many studies have investigated the effectiveness of behavioral modifications, and cognitive rehabilitation in delaying the onset of cognitive decline. Interventions include the use of memory aids, music, videotapes, sensory stimulation and relaxation. These strategies have been applied and shown to be of varied effectiveness for patients in nursing homes or long-term care facilities,[116] and are beginning to be evaluated in community and home care settings.

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[109] Ott and Owens, *Complementary and Alternative Medicines*.

[110] D.L. Bai, X.C. Tang, and X.C. He, "Huperzine A, A Potential Therapeutic Agent for Treatment of Alzheimer's Disease," *Current Medicinal Chemistry*, vol. 7, 2000, pp. 355-374 (Hereafter cited as Bai et al., *A Potential Therapeutic Agent*).

[111] Ott and Owens, *Complementary and Alternative Medicines*.

[112] Bai et al., *A Potential Therapeutic Agent*.

[113] Ott and Owens, *Complementary and Alternative Medicines*.

[114] Ian G. McKeith, *Alzheimer's Society Information Sheet*, Nov. 2000. Available at [http://www.alzheimers.org.uk/print_info/p_drugsbehaviour.htm].

[115] Cummings, "Alzheimer's Disease."

[116] Ibid.

Diagnosis

Definitive diagnosis of AD is only possible upon death of the individual and confirmation of the physical signs of AD pathology. These findings include gross or microscopic evidence of beta-amyloid plaques, neurofibrillary tangles, degeneration of small blood vessels, and neuronal loss.

Diagnosis of probable or possible AD while an individual is alive is based on differential exclusion of other possible causes for the symptoms.[117] Neuropsychological evaluation and cognitive testing by psychologists are the preferred differential diagnostic methods to discriminate organic dementia from age-related cognitive decline, cognitive difficulties related to depression and other related disorders.[118] Initial assessments typically include evidence of functional decline in multiple cognitive domains (not just memory); a focused history and physical examination (to take into account any sensory impairment or confounding factors); informant reports (family, friends and caregivers); mental tests; and an evaluation of mental health status.[119] These laboratory, functional, and cognitive tests are conducted to first rule out other causes of dementia, such as: vascular dementia, Picks Disease, HIV infection, head trauma, substance abuse, or other mental or systemic illness.

"Probable" AD is determined by a diagnosis of progressive dementia on the basis of the Mini-Mental State Test or similar examination of cognitive function that cannot be explained by the presence of another disorder based on neuropsychological tests. Probable AD patients have deficits in at least two areas of cognition. "Possible" AD is used when the a patient has dementia that cannot be explained by another cause, and a deficit in only one area of cognition.[120] Using the criteria of McKhann (1984), probable AD is confirmed at autopsy with 85%-90% accuracy.[121] These criteria were reviewed by the Quality Standards Subcommittee of the American Academy of Neurology in 2001 and found to be reliable.[122]

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[117] M.B. First, ed., "Delerium, Dementia, and other Cognitive Disorders," *Diagnostic and Statistical Manual of Mental Disorders, 4th edition* (Washington, DC: American Psychiatric Association, 1994), pp. 134-155.

[118] APA Presidential Task Force on the Assessment of Age-Consistent Memory Decline and Dementia, *Guidelines for the Evaluation of Dementia and Age-Related Cognitive Decline*, Feb. 1998. Available at [http://www.apa.org/practice/dementia.html].

[119] *Early Alzheimer's Disease: Recognition and Assessment*, Sept. 1996. Available at [http://www.ahcpr.gov/clinic/alzover.htm].

[120] G. McKhann, et al., "Clinical diagnosis of Alzheimer's Disease: Report of the NINCDS-ADRDA Work Group," *Neurology*, vol. 34, July 1984, pp. 939-944.

[121] D. Galasko, et al., "Clinical-Neuropathological Correlations in Alzheimer's Disease and related dementias." *Archives of Neurology*, vol. 51, no. 9, Sept. 1994, pp. 888-895.

[122] D.S. Knopman, et al., "Practice parameter: Diagnosis of Dementia, Report of the Quality Standards Subcommittee of the American Academy of Neurology," *Neurology*, vol. 56, 2001, pp. 1143-1153.

Current research efforts are largely focused on improving mechanisms of patient assessment such as imaging techniques, genetic testing, and assessment of environmental risk factors to better understand physical changes in the AD brain, and their association with familial risk and environmental exposures. The goal is earlier identification of patients at greatest risk believing that earlier identification may afford earlier opportunities for intervention.

Brain Imaging. Structural imaging of the brain is generally recommended in the routine initial evaluation of patients diagnosed with dementia to increase the accuracy of the clinical diagnosis. In many cases, brain atrophy (i.e., shrinking) can be seen on imaging tests that show structure, such as computed tomography (CT) or magnetic resonance imaging (MRI). Given that normal aging brains can have evidence of plaques and tangles, some are questioning the value of imaging (at least with the current state of technology) in diagnosing early Alzheimer's. Without an effective treatment, doctors are not likely to recommend using imaging to screen nonsymptomatic individuals for AD, despite widespread availability and marketing by commercial firms.[123] Some of the available imaging techniques are discussed below.

Computed Tomography (CT) scanning uses special x-ray equipment to produce cross sections of the body, providing detailed images of organs, bones, and other tissues. The cross-sections eliminate much of the overlap of structures and increases the resolution of imaging over traditional x-rays. Sometimes a special dye is used to increase the contrast between soft and solid body parts. The CT is used to evaluate the structure of the brain, including an assessment of its size. AD may be indicated if brain atrophy (i.e., shrinking) is seen.

Magnetic Resonance Imaging (MRI) uses radio-frequency waves and a strong magnetic field to provide remarkably clear and detailed pictures of internal organs and tissues. MRI requires specialized equipment and expertise and allows evaluation of some body structures that may not be as visible with other imaging methods.[124] The MRI also evaluates brain structure and size. While it can have better resolution than a CT scan and does not use ionizing radiation, other factors (such as the effect on implanted metal electronic devices or the long time needed to capture an image) may make MRI less desirable for some patients.

Positron Emission Tomography (PET) scans produce images based on how the brain uses glucose (sugar). In a PET scan, areas of the brain that are actively functioning or using sugar show up as red-orange spots. Dark blue or violet spots indicate little activity. AD is suspected if a dark spot shows up in an area of the brain

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[123] John Fauber, "Doctors See Brain Scans as Ripe for Abuse. Alzheimer's Fears Could Lead to Unnecessary Procedures, They Say," Milwaukee Journal Sentinel, July 4, 2004, at [http://www.jsonline.com/alive/news/jul04/245968.asp], accessed July 18, 2005.

[124] Radiology information, at [http://www.radiologyinfo.com/content/mr_of_the_body.htm].

where language and memory processing occurs. PET scans may detect early signs up to 93% of the time, at a cost of about $1,500 each.[125]

Single photon emission computed tomography (SPECT) is another test of brain function. SPECT evaluates blood flow in the brain following the injection of a special imaging solution into a patient. SPECT may be more comfortable to administer than other imaging techniques, which require that a patient be enclosed inside the detection device. Functional tests, such as PET and SPECT, can complement structural tests, like CT or MRI.

Despite promise for earlier diagnosis, most current imaging studies are limited to detecting damage which has already begun. The challenge is to untangle the early effects that are predictive for AD, while excluding normal aging or other disorders. Some new studies are focusing on using neuroimaging techniques to untangle the genetic and environmental influences of normal brain structure. Surprisingly, many physical brain features — such as the distribution of gray matter in the cerebral cortex — are under significant genetic control; where there is genetic similarity between individuals, there is similarity in brain structure during the normal aging process and in certain disease processes.[126] Structural changes — such as brain atrophy over time in patients with mild cognitive impairment — may improve diagnosis. However, the clinical value of the information over the battery of tests that are currently available remains to be established.[127]

Other studies are focusing on identifying and evaluating new early biomarkers of AD that will improve the imaging process. Biomarkers are molecules that can be tagged with a dye that can be traced through the brain with imaging studies. For example, NIA is currently recruiting for a large Neuroimaging Initiative. This study is the product of a public and private partnership to develop more biomarkers for AD. It is estimated that the research will cost approximately $12 million per year. As of July 2004, 24 companies had agreed to contribute.

Genetic Associations in Familial and Sporadic Disease. Familial AD comprises about 25% of all cases of the disease. Heritable causes of AD are still largely unknown. In early onset familial AD, the disease appears to be inherited in an autosomal dominant fashion, where the risk of transmission between a parent with AD to his/her child is 50%.[128] Early onset AD has three subtypes of disease, depending on what gene is involved. AD1 is caused by a mutation in the amyloid precursor protein (APP) gene, AD3 by a mutation in the presenilin-1 (PSEN1) gene,

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[125] Daniel H.S. Silverman, et al., "Positron Emission Tomography in Evaluation of Dementia: Regional Brain Metabolism and Long-term Outcome," *Journal of the American Medical Association*, vol. 286, no. 17, Nov. 7, 2001, pp. 2120-2127.

[126] Paul Thompson, et al., "Genetic Influences on Brain Structure," *Nature Neuroscience*, Dec., vol. 4, no. 12, 2001, pp. 1-6.

[127] P.J. Nestor, P. Scheltens, and J.R. Hodges, "Advances in the Early Detection of Alzheimer's Disease," *Nature Reviews Neuroscience*, July 2004, pp. S34-S41.

[128] Bird, *Alzheimer Disease Overview*.

and AD4 by a mutation in the presenilin-2 (PSEN2) gene.[129] All of these genes may impact how beta-amyloid is produced or cleared.[130] "Presenilin" is a generic term for a family of proteins that are found in all cell types and are highly conserved between species. Though not proven, the gene for presenilin is thought to code for secretase, an enzyme(s) that cleaves APP to produce the beta-amyloid peptide found in AD plaques[131] or for an unidentified protein that may regulate secretase.[132]

Table 6. Familial AD: Genetic Associations and Frequency of Occurrence

Disease subtype	Major associated gene (gene locus [a])	Frequency
Early Onset Subtypes		
AD1	APP (21q21)	10%-15%
AD3	PSEN1 (14q24.3)	20%-70%
AD4	PSEN2 (1q31-q42)	rare
Late Onset AD		
AD2	ApoE4 (19q13.2)	46%[b]

Source: Bird, *Alzheimer Disease Overview*.

a. The gene locus refers to the physical location of a gene on a chromosome. Standard nomenclature is to put the chromosome number first, followed by the chromosome arm, and then by band where the gene is located. For example, the APP gene locus is 21q21. This means that the gene is located on chromosome 21, the q (or long) arm, band number 21. Knowing the gene locus can be important for researching what other disease or health-related genes may be located in the same area (i.e., some genetic damage can affect multiple genes and cause multiple conditions simply because the genes are close together).

b. This statistic is interpreted as 46% of patients with AD and a family history of AD have at least one ApoE4 allele, in either a homozygous e4/e4 (i.e., the e4 allele is on both chromosomes) or heterozygous state (i.e, e4 on one chromosome, and another ApoE allele on the other).

[129] Summarized in On-line Mendelian Inheritance in Man (OMIM), *#104300, Alzheimer Disease*, July 31, 2003. Available at [http://www.ncbi.nlm.nih.gov/omim/] (Hereafter cited as OMIM, *#104300 Alzheimer Disease.*)

[130] Kristel Sleegers and Cornelia M. van Duijn, "Alzheimer's Disease: Genes, Pathogenesis and Risk Prediction," *Community Genetics*, vol. 4, 2001, pp. 197-203.

[131] Selkoe, *Alzheimer's Disease: Mechanistic Understanding*.

[132] Rosenberg, *The Molecular and Genetic Basis of AD.*

For late onset familial AD, the mode of inheritance is unknown. Late onset AD is thought to involve multiple susceptibility (i.e., risk increasing) genes. If someone in a family is identified as having late onset AD, the risk to other first degree relatives is 15%-30%.[133] The major gene involved with late onset familial disease is ApoE. ApoE does not cause AD, but is associated with an increased risk for developing AD. People with two copies of the ApoE4 allele represent only 2%-3% of the general population, but 15%-20% of the AD population.[134] Another allele, ApoE2, is rarely found in AD patients, and may confer a protective effect.[135] ApoE3 is most commonly found in the non-AD population. Individuals with two copies of ApoE4 allele have an eight-fold risk of developing AD by age 75 while individuals with one copy of the allele have a three-fold increase in risk.[136]

Candidate genes for sporadic late onset disease have been elusive. It is possible that the genes for the proteins involved in cholesterol metabolism in the neuron — such as alpha-2-macroglobulin, low density lipoprotein receptor, ApoE4 and amyloid precursor protein described earlier — may participate in a common pathway that leads to the AD-related neurodegeneration.[137] The genes for alpha-2-macroglobulin and the low density lipoprotein receptor are on chromosome 12. Several studies have shown linkage between sporadic AD and chromosome 12, but the actual gene involved has been elusive.[138] A gene on chromosome 10 may influence the age of onset of AD.[139] So far, there have been no associations between mutations in the tau gene (associated with neurofibrillary tangles) and familial AD;[140] however, in a mouse model, a gene called PIN1 has been recently identified that may protect against AD, coding for a protein that may 'untangle' tangles caused by the tau protein.[141]

Genetic Tests. Genetic testing can offer benefits as well as risks. Perhaps the greatest benefit of using predictive testing in asymptomatic (i.e., healthy) adults is the opportunity to prevent damage before it occurs. As more genes are found to

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[133] Bird, *Alzheimer Disease Overview*.

[134] American College of Medical Genetics (ACMG), "Statement on Use of Apolipoprotein E Testing for Alzheimers Disease," *Journal of the American Medical Association* , vol. 274, 1995, pp. 1627-1629. Available at [http://www.acmg.net/resources/policies/pol-001.asp], accessed July 18, 2005 (Hereafter cited as ACMG, Statement on Use of Apolipoprotein).

[135] Bird, *Alzheimer Disease Overview*.

[136] Rosenberg, *The Molecular and Genetic Basis of AD*.

[137] OMIM, *#104300 Alzheimer Disease*.

[138] Rosenberg, *The Molecular and Genetic Basis of AD*.

[139] Testimony of NIA Director Richard Hodes, in U.S. Congress, Senate Committee on Health, Education, Labor and Pensions Subcommittee on Aging, *Breakthroughs in Alzheimer's Disease: News You Can Use*, hearing, 108th Congress, 2nd session, May 11, 2004, at [http://help.senate.gov/testimony/t95_tes.html].

[140] Some studies have shown that mutations in the tau gene are associated with a form of frontotemporal dementia. See Selkoe, *Alzheimer's Disease: Mechanistic Understanding*.

[141] Y.C. Liou, et al., "Role of the Prolyl Isomerase PIN1 in Protecting Against Age-dependent Neurodegeneration," *Nature*, vol. 424, no. 6948, 2003, pp. 556-561.

cause disease, testing may allow an individual to prepare for the eventual disability associated with disease, and studying them will improve the understanding of disease etiology, progression and pathology. Susceptibility testing does not identify which individuals will eventually get the disease, but it can provide information about individuals who are at higher risk for developing AD, so that those individuals may avoid other environmental factors that may further increase their risk. Pharmacogenetic or pharmacogenomic testing[142] may eventually help to identify people who could benefit from new drugs, or from genotype specific dosing regimens for old or new drugs.

The risks of testing asymptomatic adults include a possible negative effect on personal relationships and emotional well-being for those who test positive, and may offer a false sense of security for those who test negative. Clinical laboratory tests are available for ApoE4, APP, PSEN1 and PSEN2.

A consensus statement of the American College of Medical Genetics (ACMG), the American Society of Human Genetics (ASHG), the American Academy of Neurology (AAN) and the American Pediatric Association (APA) agreed that although there is strong association between AD and ApoE4, testing is not recommended for the general population. The statement stressed that susceptibility or predictive testing is only valuable if the course of the condition can be affected by lifestyle changes or early drug intervention (prevention or alleviation).[143] Others feel that although testing for the ApoE4 allele is not widely recommended, identification of the e4/e4 genotype may increase the sensitivity of traditional diagnosis up to 97% in a symptomatic patient with family history of dementia. Diagnostic testing of asymptomatic family members for PSEN1, APP, or PSEN2 is only recommended if a mutation has already been identified in a family member with Alzheimer's.[144]

Once a mutation is known in a family to be associated with a disease, testing in other situations — such as in prenatal or preimplantation diagnostic testing[145] — is possible. Prenatal testing for PSEN1, PSEN2 and APP mutations is possible for families where a mutation has been identified in association with disease. However,

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[142] Pharmacogenetic testing investigates variations that are inherited in a person's DNA that are associated with how that individual's body reacts to drugs. Studies in pharmacogenetics generally look for markers that will predict whether an individual will have an adverse reaction to a drug, but can also investigate other aspects of drug metabolism. Pharmacogenomic testing looks at the entire complement of gene products (including proteins and enzymes) that are expressed in association with an individual's reaction to specific drugs.

[143] ACMG, *Statement on Use of Apolipoprotein*.

[144] Bird, *Alzheimer Disease Overview*.

[145] Prenatal diagnosis is a process by which a sample of fetal cells is collected from a pregnant woman through a procedure called amniocentesis, which relies on a needle being inserted into the uterus during pregnancy. The cells can be cultured and analyzed for genetic diseases or conditions for which the cause is known. Preimplantation diagnosis involves the examination of products of conception (such as an early cell from a developing embryo) or other by-product of *in vitro* fertilization (IVF), for genetic diseases or conditions. Only embryos lacking the genetic disease gene are implanted in the uterus.

GeneTests (an online resource for locating genetic testing laboratories and associated services) reports that no labs are offering testing for that purpose. Generally, requests for prenatal testing for adult conditions is uncommon, and is not supported by professional associations.[146] Despite the recommendations, there was a report of a case of preimplantation diagnosis in a mother with an APP mutation. The consensus of the professional community is not to test children for adult onset diseases because of the possibility of stigmatization, or serious educational and career implications.

Investigational Treatments

New Compounds. PhRMA, a leading association for pharmaceutical manufacturers, indicates that there are 25 drugs under investigation for AD (excluding the agents used in gene therapy); five have been approved by FDA either for AD or other indications (i.e., they are already on the market).[147] Of the 20 unapproved products, only three (Alzhemed, Ampalex/CX516, and NS 2330) are registered with the federal government. See [http://www.clinicaltrials.gov].[148] It is too soon to tell which, if any of these new treatments will be effective in treating AD. However, to put this research in the context of what is already available (refer to section *Physiological* Changes and Pharmaceutical Targets), of the remaining 17 new compounds currently under investigation:

- 2 compounds target beta-amyloid formation, aggregation or clearance (one is an alternate form of an anti-inflammatory drug);
- 1 compound is thought to inhibit neuroinflammation;
- 1 compound modulates calcium channel activity;
- 2 compounds affect the acetylcholine neurotransmitter system;
- 2 compounds are neurotrophic (i.e., "nerve growing") agents;
- 2 compounds are monoamine oxidase inhibitors (one of which also has anti-acetylcholinesterase activity and neuroprotective activity);
- 3 compounds target mood, anxiety and/or behavioral symptoms; and
- 4 have an unknown, unspecified or unpublished mechanism of action.

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[146] ACMG, *Statement on Use of Apolipoprotein*.

[147] PhRMA *Medicines in Development for Older Americans*, at [http://www.phrma.org/newmedicines/].

[148] Companies are required to inform the federal government that they plan to conduct clinical trials by filing an Investigational New Drug (IND) application with the FDA. Once approved, companies are also supposed to disclose the existence of many ongoing clinical studies to the federal government in a database, such as [http://www.clinicaltrials.gov]. Despite this requirement, few companies actually submit information to the database. A *Washington Post* article noted that only 13% of the 5,754 trials listed in the federal clinical trials database, ClinicalTrials.gov, were industry sponsored, in contrast to estimates that over 80% of trials are funded by for-profit companies. See Shankar Vedantam, "Drugmakers Prefer Silence on Test Data," *Washington Post*, July 6, 2004, p. A01. See CRS Report RL32832, *Clinical Trials Reporting and Publication*, by Erin Williams.

Gene Therapy. Gene therapy is a procedure that uses genetically modified cells (from the patient or another source) or infectious agents to: introduce normal genetic sequences to replace deficient ones; to selectively kill certain cells (e.g., diseased cells); to make a body cell resistant to different types of infection (e.g., HIV infection) or to stimulate a patient's immune function.[149] Gene therapy trials must be approved by both the FDA (for use of the investigational therapeutic agent) and the NIH Recombinant DNA Advisory Commitee (RAC) (for important human factor considerations and technical review) prior to initiation.

In 2001, doctors at the University of California, San Diego (UCSD) performed the first surgery to implant genetically modified tissue into the brain of an AD patient. In the therapy, skin samples from the patient (who had early-stage Alzheimer's) were collected and modified in the laboratory to introduce genes for nerve growth factor (NGF). After the researcher verified that the cells produced the NGF, they used a surgical procedure to implant the modified cells in damaged areas of the brain. A total of eight people underwent the procedure, and were followed for a year.[150] No adverse events were noted in any of the patients one year after surgery. PET imaging of the patients showed increased metabolic activity in the areas of the brains of patients after the treatment with NGF, and an autopsy of a patient who died (death not related to treatment) showed active NGF production in the brain, with a growth response of brain cells to the NGF delivery.[151]

A second trial is underway by researchers at Rush University Medical Center and sponsored by Ceregene, Inc. to evaluate the safety, tolerability, and efficacy of a new agent, CERE-110, in subjects with mild to moderate AD. CERE-110 is a commercially developed agent that uses an adeno-associated virus to deliver NGF to brain cells.[152] The CERE-110 trial is listed with the federal government, at [http://www.clinicaltrials.gov].

Stem Cells and Tissue Regeneration. Stem cells are cells within the body that have not yet become specialized to perform a single function (i.e., they are not blood, nerve, skin, muscular, etc). There are two types of stem cells: adult and embryonic. Adult stem cells circulate the body in low numbers, and retain the ability to become a specialized cell if needed. Much research has focused on harvesting and using adult stem cells to repair tissue damage (such as spinal cord injury and brain damage). Embryonic stem cells are derived from an early stage embryo. Though

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[149] P.M. Cannon and W.F. Anderson, "Retroviral Vectors for Gene Therapy," in NS Templeton and D.D. Lasic eds., *Gene Therapy Therapeutic Mechanisms and Strategies* (New York, NY: Marcel Dekker, Inc., 2000), pp. 1-16.

[150] See *Gene Therapy for Alzheimer's Disease — Clinical Trial Information*, at [http://tuszynskilab.ucsd.edu/clinical_study.htm].

[151] See *Preliminary Results Are Promising in Alzheimer's Gene Therapy Trial*, online at [http://www.eurekalert.org/pub_releases/2004-04/uoc — pra042204.php].

[152] See protocol number 0401-623, "A Phase I/II, Dose-Escalating, Randomized and Controlled Study to Assess the Safety, Tolerability, and Efficacy of Cere-110 [Adeno-associated Virus (Aav)-based, Vector-mediated Delivery of Beta-nerve Growth Factor (Ngf)] in Subjects with Mild to Moderate Alzheimer's Disease," at [http://www.gemcris.od.nih.gov].

they may have a greater potential to become different types of cells than adult stem cells, research using them is highly controversial, currently prohibited to existing lines, and is the subject of heated debate in Congress.[153]

Despite the controversy, some scientists believe there is potential for use of stem cells in AD.[154] Much of the federally funded research aims at further understanding the mechanisms and regulation of how neural stem cells (NSC) differentiate into specialized neurons. There are major barriers to overcome before stem cell therapy can become a clinical reality in the treatment of AD. Because memory deterioration involves the degeneration of specific cells (cholinergic neurons), scientists have to figure out how to replace a specific cell type (see also the section, "Neurotransmitters"). This is complicated because the beta-amyloid formation process in the diseased brain may create an environment that influences what type of cell the NSC becomes.[155] Two studies currently underway are focusing on using NSCs to repair damage to AD brains in an animal model.[156] Given the scientific and political barriers, clinical therapies using stem cells — while promising — are not likely to be available in the near term.

The National Human Neural Stem Cell Resource provides neural stem cells harvested from the post-natal, post-mortem, human brain to the research community for stem cell research. Several brain areas as well as cultures from normal and genetically mutant specimens are represented in the Resource.[157]

Vaccination. Because evidence suggests that the formation of plaques may elicit an immune response, researchers have hypothesized that antibodies against beta-amyloid may either prevent its accumulation or facilitate its clearance by launching an immune attack against the plaque. Despite early promise, a clinical trial of active vaccination against beta-amyloid had to be stopped due to complications. Following the trial, analysis of a small group of patients suggested that vaccination resulted in a reduction in disease progression in patients whose bodies generated antibodies against the beta-amyloid.[158] Given this promise, some scientists believe

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[153] More a more detailed discussion of stem cells and the debate concerning the use of stem cells in research, see CRS Report RL31015, *Stem Cell Research*, by Judith A. Johnson and Erin Williams.

[154] Statement of Richard J. Hodes, Director, National Institute on Aging, in U.S. Congress, Senate, Subcommittee of the Committee on Appropriations, *Alzheimer's Disease, 2003* hearings, 108th Cong., Mar. 23, 2004, S.Hrg. 108-130, [http://frwebgate.access.gpo.gov/cgi-bin/getdoc.cgi?dbname=108_senate_hearings&docid=f:89018.wais.pdf].

[155] Kiminobu Sugaya, "Neuroreplacement Therapy and Stem Cell Biology under Disease Conditions," *Cellular and Molecular Life Sciences*, vol. 60, 2003, pp. 1891-1902.

[156] Based on a search of the CRISP (Computer Retrieval of Information on Scientific Projects) database, search terms "Alzheimer's" and "Stem Cells," accessed Aug. 25, 2004, at [http://crisp.cit.nih.gov/crisp/crisp_query.generate_screen].

[157] See [http://www.nhnscr.org/default.htm].

[158] C. Hock, et al., "Antibodies Against Beta-Amyloid Slow Cognitive Decline in Alzheimer's Disease," *Neuron*, vol. 38, 2003, pp. 547-554 in Cummings, *Alzheimer's* (continued...)

that passive immunization[159] may be safer. Even if immunization were successful in helping the body prevent beta-amyloid accumulation by facilitating clearance of the peptide, it is unclear whether vaccination in later life will be able to reverse cognitive defects or brain pathology.

Currently, there are no human trials of AD vaccines registered with the federal government. However, there are 15 federally funded research studies investigating new formulations of AD vaccines in mouse models.[160]

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[158] (...continued)
Disease.

[159] Active immunization is when a patient is given a vaccination consisting of an administered dose of either an infectious agent or small molecule (such as a protein) before exposure to the element, in an attempt to get the patient's immune system to make antibodies. At some future point when the patient contacts the agent (beta-amyloid), the antibodies will then fight the agent to rid the body of the harmful agent. Passive immunization is when a patient is given antibodies directly to fight an agent or molecule. Passive immunization is usually given when the patient has already been exposed to the agent.

[160] CRISP search of "Alzheimer's Vaccine," at [http://crisp.cit.nih. gov].

Appendix A. Glossary

Allele — The specific version of a *gene* that is located on a *chromosome*. Normally, individuals will have two alleles for each gene, one located on each chromosome in a set.

Amygadala — The amygdala is an almond-shaped mass of gray matter, one in each hemisphere of the brain, that is associated with feelings of fear and aggression and is important for visual learning and memory.

Amyloid precursor protein — A large protein which is cleaved into smaller proteins (or peptides), one of which is the beta-amyloid form that accumulates in the brains of patients with AD as beta-amyloid plaques.

Autosomal dominant — A mode of inheritance in which a child has a 50% chance of inheriting a particular trait, condition or disease from their parent.

Beta-amyloid — A cleavage product of amyloid precursor protein, this peptide forms a beta-pleated sheet which accumulates in the brains of AD patients as plaques.

Chromosome — A long stretch of *DNA* that contains genes and other information. Humans have 46 chromosomes, which arrange during cell division in pairs of two (23 sets). During reproduction, each parent contributes one set of 23 chromosomes to their offspring.

Dementia — A clinical state characterized by loss of mental function.

DNA — Deoxyribonucleic acid; a large, double-stranded nucleic acid molecule arranged like a staircase (double helix); the chemical substance of which genes are composed.

Early onset AD — When symptoms appear before age 65.

Enzyme — A special kind of *protein* that can cause biochemical reactions to occur.

Familial AD — Alzheimer's disease that runs in family.

Family history — A record of diseases, conditions, or traits in a nuclear (parents, children) or extended (grandparents, aunts, uncles, cousins, etc.) family.

FDA — United States Food and Drug Administration.

First degree relative — A first degree relative is defined as a parent, brother, sister or child of an individual. A second degree relative would include grandparents, aunts, uncles, nephews or nieces (children of aunts and uncles).

Gene — A stretch of DNA that carries information from one generation to the next and codes for a specific *protein*.

Genotype — The specific *alleles* (forms of genes) in a cell. For example, everyone has a gene(s) for eye color. The genotype would be the specific *alleles* that resulted in a particular *phenotype* like blue eyes.

Heterozygous — When the *alleles* (forms of a gene) on both *chromosomes* (one inherited from mother, one from father) are different.

HHS — United States Department of Health and Human Services.

Hippocampus — The hippocampus is part of the lower brain, one part within each of the cerebral hemispheres. It is concerned with basic drives, emotions, and short-term memory.

Homozygous — When the *alleles* (forms of a gene) on both *chromosomes* (one inherited from mother, one inherited from father) are the same.

Late onset AD — When symptoms appear at or after age 65.

Mode of inheritance — The pattern by which a trait, characteristic, disease, disorder or condition is transmitted from a parent to a child.

Mutation — In contrast to a *chromosome abnormality*, a mutation is an individual change in a *DNA* sequence that accounts for *genetic variations*. Mutations may be harmful if they prevent genes from making normal *gene products*. These mutations can cause, or increase susceptibility to, specific diseases or conditions. A mutation can be inherited from a person's parents, or acquired from exposure to a toxic environmental condition

Multifactorial — Multiple causes.

Neocortex — The neocortex is a thin layer of nerve cells that covers the cerebral cortex (top brain) that is involved with higher brain functions such as learning.

Neurofibrillary tangles — Neurofibrillary tangles are characteristic "flame shaped" structures in the AD brain. The tangles are accumulations of abnormal forms of tau proteins, which make up microtubules in a normal nerve cell. The microtubules are The microtubules are the structures that neurons use to carry substances within the body of the cell and to its many projections.

Neurotransmitter — A neurotransmitter is a chemical made by a nerve cell that is used to transmit signals from one neuron to either another neuron or other cell (such as a skeletal muscle cell or heart muscle cell).

Neuron — Another name for a nerve cell.

Peptide — A short or truncated protein.

Pharmacogenetic — Variations that are inherited in a person's DNA that are associated with how that individual's body reacts to drugs. Studies in pharmacogenetics generally look for markers that will predict whether an individual

will have an adverse reaction to a drug, but can also investigate other aspects of drug metabolism.

Pharmacogenomic — The entire complement of gene products that are expressed in association with an individual's reaction to specific drugs. Studies in pharmacogenomics investigate many aspects of the drug metabolism process; and many focus on identifying patterns of *gene product* expression that change in response to drug treatment, and whether those changes indicate that the drug is working.

Phenotype — Observable characteristics (appearance) of an individual that are determined by the interaction of *genes, gene products* and the environment. Phenotypic testing identifies *genetic variation* by looking at the structure or function of a gene products rather than looking directly at the gene.

Plaques — A buildup of the abnormal form of beta-amyloid in the brain which also contains various lipids and inflammatory proteins. The buildup makes a dark round spot in the brain tissue, called the plaque.

Polygenic — Multiple genes.

Predictive testing — Testing a currently healthy or asymptomatic individual's DNA for variations that may be associated with future disease.

Preimplantation diagnosis — A testing procedure performed on human eggs, sperm or embryos before implantation in the uterus to determine whether or not certain genetic disease, conditions, or traits are present.

Prenatal diagnosis — A testing procedure done on cells that are shed from a developing fetus, usually between the third and fourth month of pregnancy, to determine if the fetus has a genetic disease, condition or trait.

Protein — A string of amino acids that form a three-dimensional structure to carry out the functions of a cell. Proteins can be structural (give the cell shape), regulatory (act to turn genes "on or off"), or enzymatic (cause biochemical reactions to occur).

Secretase — An enzyme or family of enzymes that are thought to cleave amyloid precursor protein into smaller peptides, one of which is the beta-amyloid peptide found in AD plaques.

Stem cells — Unspecialized cells in an adult organism or embryo that have the potential to become differentiated into any kind of functional cell (e.g., nerve, muscle, blood).

Susceptibility — A possibility of disease caused or influenced by a *genotype*. Most diseases result from a complex set of both genetic and environmental causes. Some harmful gene mutations increase the likelihood that a person will develop a specific disease.