

NIH Centers of Excellence

Alzheimer's Disease Centers

Overview

Why the ADCs Were Established

In 1984, Congress directed NIH to foster further research related to Alzheimer's disease (AD). The NIH [Alzheimer's Disease Centers](#) (ADCs) program is authorized by the Public Health Service Act under section 445 (42 U.S.C. 285e-2). The first ADCs were funded in the mid-1980s in response to the congressional directive and knowledge of AD pathophysiology emerging from the work of NIH grantees and other researchers. The prospect of a medical and social crisis triggered by an explosion of AD cases in a rapidly increasing aged population also motivated their creation. The principal objectives of the ADC program are to promote research, training, and education; technology transfer; and multicenter and cooperative studies of diagnosis, treatment, and clinico-neuropathological correlations in AD, in age-related neurodegenerative diseases, and in normal aging.

How the ADCs Function Within the NIH Framework

There are currently 29 ADCs funded by NIH (see Table 4-1). The centers are funded under the P30 and P50 mechanisms for 5 years and then must compete through a peer review process for additional funding. New applicants for ADCs compete with existing grantees, and if existing centers are unsuccessful in competition, new centers are funded to take their places.

Description of Disease or Condition

[AD](#) is the most common form of dementia among older people. It is a neurodegenerative disease that damages the parts of the brain controlling thought, memory, and language. AD is named after Dr. Alois Alzheimer, a German doctor who, more than 100 years ago, studied the brain tissue of a woman who had died of an unusual mental illness, and found abnormal clumps (now called amyloid plaques) and tangled bundles of fibers (now called neurofibrillary tangles). Today, these plaques and tangles in the brain are considered signs of AD, as are other brain changes, including the death of nerve cells in areas of the brain that are vital to memory and other mental abilities and the disruption of functional connections, called synapses, that allow nerve cells to communicate with each other. The disease is also characterized by lower levels of some of the chemicals in the brain that carry messages between nerve cells. AD may impair thinking and memory by disrupting these messages.

There probably is no single cause of AD. The most important known risk factors are age and family history, although education, diet, and environment might also play roles. Scientists are also finding evidence that some of the risk factors for heart disease and stroke—such as high blood pressure, high cholesterol, and low levels of the vitamin folate—might increase the risk of AD. Evidence is also increasing for physical, mental, and social activities as protective factors against AD. Although scientists have learned a great deal about AD, they still do not know what causes the disease and have not identified a cure for it.

Burden of Illness

AD is estimated to affect approximately 4.5 million older people in the United States¹ and 24.3 million people worldwide². Although it is occasionally diagnosed in patients in their forties and fifties, AD most frequently is associated with advancing age. The disease doubles in prevalence with every 5 years past age 65; thus, extending life by 10 years quadruples the probability of the disease occurring. AD is the most frequent cause of institutionalization for long-term care. It destroys the active, productive lives of its victims and devastates their families financially and emotionally. It has been estimated that the United States spends as much as \$148 billion per year for the direct and indirect costs of care for patients with AD³. With the rapidly increasing percentage of the population older than 65, the number of people with AD will increase proportionately, as will the toll it takes.

Scope of NIH Activities: Research and Programmatic

The ADC program provides an environment and core resources to enhance ongoing research by bringing together biomedical, behavioral, and clinical science investigators to study the etiology, progression, prevention, diagnosis, and treatment of AD and to improve health care delivery. ADCs also foster the **development** of new research approaches and provide suitable environments for research fellows and junior faculty to acquire the necessary skills and experience for interdisciplinary AD research.

All 29 ADCs are required to have an administrative core, a clinical core, a data management and statistics core, an education and information transfer core, and a neuropathology core. Some centers include other, optional cores, such as neuroimaging or genetics cores, and some have satellite diagnostic and treatment clinics to assist in the recruitment of minority research subjects. The ADC program comprises two types of centers: Alzheimer's Disease Research Centers (ADRCs) conduct research projects in addition to core resources, and the Alzheimer's Disease Core Centers (ADCCs) consist of cores only and provide access to investigators with well-characterized patients, patient and family information, and tissue and other biological specimens for use in separately funded research projects.

By pooling resources and working cooperatively, the ADCs have produced research findings and developed resources that could not have been achieved by individual investigators working alone. Biological samples from patients with AD have provided the materials for hundreds of non-ADC funded projects. Several major longitudinal studies on the development of dementia in particular populations rely on ADC core facilities and integrate their findings with those of the centers. Examples of shared resources are the brain and specimen banks at each center, which consist of well-characterized specimens collected under standardized protocols. Another resource is the National Cell Repository for Alzheimer's Disease (NCRAD), located at Indiana University, which collects and stores blood, well-documented phenotypic data, DNA, and cell lines from families that have multiple affected members. The repository is part of the National Institute on Aging's (NIA's) [Alzheimer's Disease Genetics Initiative](#) to identify genetic risk factors for late-onset AD. The ADCs have spawned other collaborative efforts that have led to the establishment of research resource entities, such as the [Consortium to Establish a Registry for Alzheimer's Disease](#), the [National Alzheimer's Coordinating Center](#), the [Alzheimer's Disease Cooperative Study](#), and the [Alzheimer's Disease Neuroimaging Initiative](#) (see below.)

¹ [Hebert LE, et al. *Arch Neurol* 2003;60:1119-22](#), PMID: 12925369

² [Ferri CP, et al. *Lancet* 2005;366:2112-7](#), PMID: 16360788

³ For more information, see http://alz.org/national/documents/PR_FFfactsheet.pdf

Much important progress in AD research in the United States during the past 20 years stems from research conducted at the ADCs, as well as from resources and infrastructure provided by the centers. Advances include the linkage and cloning of mutant genes on chromosomes 1, 14, and 21, the presence of which could result in early-onset, familial Alzheimer's disease, and on chromosome 17 in frontotemporal dementia, another common cause of dementia. More recent studies have revealed the importance of the abnormal processing of proteins encoded by these genes and the identification of a specific version of a gene at a location on chromosome 19 as a risk factor for late-onset AD.

ADC scientists have conducted much of the research on protein processing related to plaque and tangle formation, including the discovery of a protein implicated in the pathogenesis of Lewy body dementia—and the recognition of the common properties of the abnormal proteins associated with several neurodegenerative diseases. Important studies relating changes in brain structure to different clinical stages of AD are being carried out in many ADCs, using patients enrolled in the clinical cores, brain imaging studies supported by imaging cores, and autopsy evaluations in neuropathology cores. In recent years, researchers have focused on evaluating cognitive changes associated with normal aging and the transitions to mild cognitive impairment and early dementia, as well as studies to identify factors that contribute to changes in cognitive abilities. Relationships and commonalities between AD and other neurodegenerative diseases are also being emphasized along with studies of contributions of non-neurological comorbid conditions.

NIH Funding for FY 2006 and FY 2007

NIH funding for the ADCs was \$49.6 million in FY 2006 and \$50.1 million in FY 2007.

Outcomes: FY 2006 and FY 2007 Progress Report

Programmatic Accomplishments

Recent programmatic accomplishments for the ADCs include the following examples.

- [National Alzheimer's Coordinating Center \(NACC\)](#): Beginning in 1999, the NACC was established to facilitate collaborative research and to standardize procedures among the 29 ADCs. NACC developed and maintains a large relational database of standardized clinical and neuropathological research data collected from each ADC. This database provides a valuable resource to qualified research scientists for both exploratory and explanatory AD research. The data provided by NACC will permit large studies that use patient samples from diverse populations and multiple ADCs. One goal is to standardize procedures among the ADCs in several ways: (1) the approach to diagnosis of AD; (2) the approach to followup with those who have the disease; and (3) the collection of common data elements, also known as the uniform dataset. Although the unique aspects of the individual ADCs will be preserved, a core of common elements will help promote communication among the ADCs as well as with non-ADC researchers and the public. Autopsy confirmation of many of the cases makes these aggregate data especially valuable.
- [Alzheimer's Disease Cooperative Study \(ADCS\)](#): The ADCS is a major AD clinical trials effort that has grown out of the ADC program. This consortium was initially funded in 1991 to test the safety and efficacy of compounds of little interest to large pharmaceutical companies and to evaluate treatments for cognitive and behavioral symptoms of AD. The trials include drugs that are off-patent, were patented and marketed for another use but might be effective in AD, or novel compounds from individual investigators or small companies that lack adequate resources to conduct clinical trials. The ADCS helps to facilitate the testing of new drugs for the treatment of AD and functions as part of the AD Prevention Initiative, which was established to invigorate

efforts to discover new treatments, risk factors, methods of early detection, and diagnosis of AD. The ADCS also develops strategies for improving patient care and alleviating caregiver burdens and expedites movement of promising new treatments and prevention strategies into clinical trials. The ADCs serve as performance sites for the ADCS.

- [Alzheimer's Disease Neuroimaging Initiative \(ADNI\)](#): ADNI is an innovative public-private partnership for examining the potential for serial magnetic resonance imaging (MRI), positron emission tomography (PET), or other biomarkers to measure earlier, and with greater sensitivity, the development and progression of mild cognitive impairment and AD. Most ADCs participate in the ADNI. Early results suggest that researchers may be able to reduce the costs associated with clinical trials by improving imaging and biomarker analysis. As part of the ADNI study, a standard physical model (i.e., a plastic phantom) was developed to monitor the performance of MRI scanners at multiple clinical sites, ensuring the accuracy of the MRI images. In another preliminary analysis, investigators compared changes over time in PET scans of brain glucose metabolism in people with normal cognition, mild cognitive impairment, and AD. They found that scans correlated with symptoms of each condition and that images were consistent across sites, suggesting the validity of PET scans for monitoring the effectiveness of therapies in future clinical trials. More than 200 researchers, as well as other interested individuals, have already accessed a public database containing thousands of brain images and related clinical data obtained through blood and cerebrospinal fluid analyses.
- **Late-Onset Alzheimer's Disease (LOAD) Genetics Initiative**: NIH launched the LOAD Genetics Initiative in 2002 to help advance AD-related genetics research. Eighteen ADCs participate in the initiative. The goal is to collect samples from 1,000 families having at least 2 members with late-onset AD as well as 1,000 control subjects. The Columbia University ADRC serves as the coordination center for the Genetics Initiative. As of 2007, more than 3,000 new blood samples from approximately 400 late-onset AD families have been sent to NCRAD. To complete enrollment, characterization, and followup of patients and control subjects in the Genetics Initiative, NIH awarded a resource grant to a group of six ADCs, which formed a consortium. In 2006, the NIH Center for Inherited Disease Research performed whole-genome scans on approximately 2,500 samples from members of these families. An article based on analysis of these [data](#) will be published in summer 2008.
- **Overlapping Dementing Diseases**: NIA and the National Institute of Neurological Disorders and Stroke (NINDS) are exploring the overlap of Parkinson's disease dementia, dementia with Lewy bodies, and AD, as well as the contributions of cerebrovascular disease to the brain pathology seen in AD. Joint initiatives in these overlap areas are under way. The ADCs collaborate with the NINDS-supported Udall Parkinson's Disease Centers to further the goals of examining the overlapping scientific and clinical issues related to AD, dementia with Lewy bodies, frontotemporal dementia, and Parkinson's disease dementia.
- **ADCs Minority Outreach**: A major objective for the ADCs is to recruit minority and ethnically diverse research subjects for AD research. A strategy to address this goal was developed in 1990 by creating a program to add Satellite Diagnostic and Treatment Clinics linked to existing ADCs. The number of satellites has fluctuated; 23 are currently active and are recruiting African American, Hispanic, Native American, and Asian research subjects. NACC data now show that approximately 20 percent of those enrolled in the ADCs are minorities.
- **Education Outreach**: All ADCs have Education and Information Transfer Cores (EITC) that support the development of clinical and research skills related to AD for physicians and other professional staff, as well as outreach to the public, including caregivers. EITC efforts have recently been redefined to emphasize subject recruitment for projects such as the NIA Genetics Initiative, ADCS, ADNI, and other clinical trials and initiatives. Collaborations include ongoing interactions with groups such as the Alzheimer's Association and the NIA's [Alzheimer's Disease Education and Referral Center](#). The ADCs pay special attention to issues of cultural sensitivity, and, where appropriate, the information is structured so it can effectively reach minority populations, including non-English-speaking people. ADCs work with ADEAR to develop materials for broad audiences.
- [New York Consortium for Alzheimer's Research and Education \(NYCARE\)](#): The three New York City ADCs—at Columbia University, Mount Sinai School of Medicine, and New York University—and the New York City

chapter of the Alzheimer's Association joined in 2000 to form NYCARE. The consortium provides continuing medical education programs for community physicians on AD diagnosis, management, and research opportunities.

- **The Alzheimer's Clinical Research and Training Awards Act:** This congressional initiative helps train the next generation of physician-scientists to conduct basic and clinical research on AD and associated dementias. The program provides support for promising clinicians through awards for research, study, and practice at the ADCs. Twelve awards have been made, and most of the awardees are working at ADCs.

Research Accomplishments

Since the establishment of the ADC program in 1984, thousands of research papers have been published on all aspects of AD and related neurodegenerative disorders, ranging from the molecular biology of the disease to family and societal impact, and including many studies of diagnosis and treatment. Research accomplishments include the following important recent studies carried out by ADC scientists.

- **Amyloid-beta Protein Metabolism Studies.** Biochemical, genetic, and animal model evidence implicates amyloid-beta as a pathogenic peptide in AD that can lead to abnormal communication among nerve cells and cell death. In late-onset AD, concentrations of this peptide in brain tissue from AD patients are 100- to 200-fold higher than in control brains. Recently, investigators at the Washington University ADC reported a new method for quantifying the synthesis and clearance rates of amyloid-beta in the normal human adult central nervous system. For the first time, investigators can now accurately measure the production and clearance rates of amyloid-beta in the central nervous system of living humans, indicating that under normal circumstances it is rapidly produced and cleared from the central nervous system. This new technique may prove to be of critical importance to scientists in their efforts to address crucial questions about the underlying pathogenesis of AD, to find possible biomarkers, and to test proposed disease-modifying therapies.
- **Standards for Assessing Cognitive Status in Understudied Populations:** One difficulty in evaluating the cognitive status of people in understudied populations is that the normative values available for standard tests often are not appropriate for other populations. Cultural, linguistic, educational, and other factors differ among groups and consistently have been shown to influence neuropsychological evaluations. Recently, scientists at the Mayo Clinic ADC produced a large set of normative data on older African Americans, using several common neuropsychological assessment tools. The authors note that these normative values may be applicable only to older African Americans raised in the South, making it important to determine whether the new data can be generalized. In addition, over time, even a narrowly defined group might have different characteristics; for example, participants in this sample were educated prior to the Brown vs. the Board of Education decision by the U.S. Supreme Court to end segregation of public school systems. Despite some limitations in its clinical utility, this study represents the first large-scale publication of normative data for an understudied population.
- **Establishing Commonalities Between Frontotemporal Dementias and Amyotrophic Lateral Sclerosis:** Frontotemporal dementias (FTDs) are a group of neurodegenerative diseases that are sometimes misdiagnosed as AD or related dementing disorders. It is estimated that 35-50 percent of FTD cases have a family history of dementia; nearly half have been linked to a mutation on chromosome 17. In recent studies, researchers have linked some cases of FTD to another mutation on chromosome 17. In addition, a new brain protein has been identified, related to the pathogenesis of both FTD and amyotrophic lateral sclerosis (ALS), in which dementia also can occur. It is thought that changes caused by this mutation impair the ability of the cell to degrade abnormal proteins, thereby causing them to remain in the nervous system, where they contribute to the development of FTD and ALS disease processes. Investigators are continuing to study these proteins and other genetic mutations to further identify and understand the mechanisms involved in the development

of FTD, ALS, and other neurodegenerative diseases.

Recommendations for Improving the Effectiveness, Efficiency, and Outcomes of the ADCs

Since their launch in 1984, the NIH ADCs have continued to grow, and many multiple-center initiatives have emerged. In 2002, NIA organized a meeting to help determine the future of the ADC program. Several recommendations were made based on this meeting and have been implemented.

The first recommendation was to create the uniform dataset, which was described earlier in this chapter (see National Alzheimer's Coordinating Center [ADCC]). Another recommendation was to encourage greater flexibility in the structure of ADCs to take better advantage of local strengths, interests, and expertise. For example, ADCs can now enroll and follow special patient populations rather than using only clinic populations, as had been required previously. ADCs also are encouraged to develop programs that change with the scientific knowledge base and to find ways to translate new knowledge into clinical applications—for example, the translation of basic research findings to measure amyloid-beta production and clearance in living patients. ADCs also are being encouraged to make better use of tissue and data resources and to share them. One example of this is the further development and expansion of NCRAD to increase its capacity to bank cell lines, DNA, and serum from all ADCs as well as other sources.

Evaluation Plans

The ADCs were reviewed in great detail by an external advisory committee in 2002 and again in less detail by the National Advisory Council on Aging in 2003. The next review by the National Advisory Council on Aging will take place in May 2008.

Future Directions

In the future, ADCs will continue to place less emphasis on late-stage AD and instead will concentrate more on the transition from normal aging to mild cognitive impairment to full-blown AD, as well as on studies that overlap with other neurodegenerative diseases. NIH will continue to support existing ADCs and to award new grants to applicant institutions that are deemed qualified through the NIH peer-review process.