

Alzheimer's Disease Centers Program Directory

The National Institute on Aging currently funds 28 Alzheimer's Disease Centers (ADC's) at major medical institutions across the nation. Researchers at these centers are working to translate research advances into improved care and diagnosis for Alzheimer's patients while, at the same time, focusing on the program's long-term goal—finding a way to cure and possibly prevent Alzheimer's disease.

Areas of investigation range from the basic mechanisms of Alzheimer's disease to managing the symptoms and helping families cope with the effects of the disease. Center staff conduct basic, clinical, and behavioral research.

Each of the 28 centers has its own unique areas of emphasis. One of the program's major benefits is the opportunity for collaborative studies that draw upon the expertise of scientists from many different disciplines.

Centers also have significant responsibilities related to information transfer and the training of scientists and health care providers new to Alzheimer's disease research. A common goal of the ADC's is to enhance

research on Alzheimer's disease by providing a network for sharing new ideas as well as research results.

Currently, 27 ADC-affiliated satellite facilities offer diagnostic and treatment services and collect research data in underserved, rural, and minority communities.

For patients and families affected by Alzheimer's disease, many ADC's offer:

- Diagnosis and medical management (costs may vary—many centers accept Medicare, Medicaid, and private insurance).
- Information about the disease, services, and resources.
- Opportunities for volunteers to participate in drug trials and other clinical research projects (and support groups and other special programs for volunteers and their families).

For more information, you may contact any of the centers on the following list directly. While the name, address, and telephone number given are for the center director, you may ask for information about any of the activities described above and about offices and satellite clinics at other locations.



Alzheimer's Disease
Education & Referral Center
PO Box 8250
Silver Spring, MD
20907-8250

800-438-4380

ALABAMA

**University of Alabama
at Birmingham**

Lindy E. Harrell, M.D., Ph.D.
Professor
Department of Neurology
University of Alabama
at Birmingham
1720 7th Avenue South
Sparks Center 454
Birmingham, AL 35294-0017
Director: Tel: 205-934-3847
FAX: 205-975-7365
Information: 205-934-9775

CALIFORNIA

University of California, Davis

William J. Jagust, M.D.
Director
University of California, Davis
Alzheimer's Disease Center
Alta Bates Medical Center
2001 Dwight Way
Berkeley, CA 94704
Director: Tel: 510-204-4530
FAX: 510-204-4524

**University of California,
Los Angeles**

Jeffrey L. Cummings, M.D.
Professor
Department of Neurology
and Psychiatry
University of California,
Los Angeles
710 Westwood Plaza
Los Angeles, CA 90095-1769
Director: Tel: 310-206-5238
FAX: 310-206-5287

**University of California,
San Diego**

Leon Thal, M.D.
Chairman
Department of Neuroscience
(0624)

University of California,
San Diego, School of Medicine
9500 Gilman Drive
La Jolla, CA 92093-0624
Director: Tel: 619-534-4606
FAX: 619-534-1437
Information: 619-622-5800

University of Southern California

Caleb E. Finch, Ph.D.
Division of Neurogerontology
Ethel Percy Andrus
Gerontology Center
University Park MC-0191
3715 McClintock Avenue
University of Southern California
Los Angeles, CA 90089-0191
Director: Tel: 213-740-1758
FAX: 213-740-0853
Information: 213-740-7777

GEORGIA

**Emory University/VA Medical
Center**

Suzanne S. Mirra, M.D.
Professor
Department of Pathology
and Laboratory Medicine
Emory University
School of Medicine
VA Medical Center (151)
1670 Clairmont Road
Decatur, GA 30033
Director: Tel: 404-728-7714
FAX: 404-728-7771

ILLINOIS

**Rush-Presbyterian-St. Luke's
Medical Center**

Denis A. Evans, M.D.
Professor of Medicine
Rush Alzheimer's Disease Center
Rush-Presbyterian-St. Luke's
Medical Center
1645 West Jackson, Suite 675
Chicago, IL 60612
Director: Tel: 312-942-3350

FAX: 312-942-2861
Information: 312-942-4463

Southern Illinois University

Robert E. Becker, M.D.
Center for Alzheimer Disease
and Related Disorders
Southern Illinois University
School of Medicine
751 North Rutledge
PO Box 19230
Springfield, IL 62794-1412
Director: Tel: 217-785-4468
FAX: 217-524-2275
Information: 800-DIAL-SIU (in IL)
or 217-782-8249

INDIANA

Indiana University

Bernardino Ghetti, M.D.
Professor of Pathology,
Psychiatry, and Medical
and Molecular Genetics
Department of Pathology,
MS-A142
Indiana Alzheimer's Disease
Center
Indiana University
School of Medicine
635 Barnhill Drive
Indianapolis, IN 46202-5120
Director: Tel: 317-274-1590
FAX: 317-274-4882
Information: 317-278-2030

KANSAS

University of Kansas

William C. Koller, M.D., Ph.D.
Professor and Chairman
Department of Neurology
University of Kansas
Medical Center
3901 Rainbow Boulevard
Kansas City, KS 66160-7117
Director: Tel: 913-588-6952
FAX: 913-588-6965

KENTUCKY

University of Kentucky

William R. Markesbery, M.D.
 Director
 Sanders-Brown Research
 Center on Aging
 University of Kentucky
 101 Sanders-Brown Building
 800 South Lime
 Lexington, KY 40536-0230
 Director: Tel: 606-323-6040
 FAX: 606-323-2866

MARYLAND

The Johns Hopkins Medical Institutions

Donald L. Price, M.D.
 Professor of Pathology,
 Neurology, and Neuroscience
 The Johns Hopkins University
 School of Medicine
 558 Ross Research Building
 720 Rutland Avenue
 Baltimore, MD 21205
 Director: Tel: 410-955-5632
 FAX: 410-955-9777

MASSACHUSETTS

**Harvard Medical School/
Massachusetts General Hospital**

John H. Growdon, M.D.
 Department of Neurology
 Massachusetts Alzheimer's
 Disease Research Center
 Massachusetts General Hospital
 WAC 830
 15 Parkman Street
 Boston, MA 02114
 Director: Tel: 617-726-1728
 FAX: 617-726-4101

MICHIGAN

University of Michigan

Sid Gilman, M.D.
 Professor and Chair
 Department of Neurology
 Michigan Alzheimer's Disease
 Research Center
 University of Michigan
 1914 Taubman Center
 Ann Arbor, MI 48109-0316
 Director: Tel: 313-936-9070
 FAX: 313-936-8763
 Information: 313-764-2190

MINNESOTA

Mayo Clinic

Ronald Petersen, M.D., Ph.D.
 Associate Professor
 Department of Neurology
 Mayo Clinic
 200 First Street SW
 Rochester, MN 55905
 Director: Tel: 507-284-4006
 FAX: 507-284-2203
 Information: 507-284-1324

MISSOURI

Washington University

Leonard Berg, M.D.
 Alzheimer's Disease Research
 Center
 Washington University Medical
 Center
 The Health Key Building
 4488 Forest Park Boulevard
 St. Louis, MO 63108-2293
 Director: Tel: 314-286-2881
 FAX: 314-286-2763
 Information: 314-286-2881

NEW YORK

Columbia University

Michael L. Shelanski, M.D., Ph.D.
 Director
 Alzheimer's Disease Research
 Center
 Columbia University
 Department of Pathology
 630 West 168th Street
 New York, NY 10032
 Director: Tel: 212-305-3300
 FAX: 212-305-5498
 Information: 212-305-8056

**Mount Sinai School of Medicine/
Bronx VA Medical Center**

Kenneth L. Davis, M.D.
 Professor and Chairman
 Department of Psychiatry
 Mount Sinai School of Medicine
 Mount Sinai Medical Center
 1 Gustave L. Levy Place,
 Box #1230
 New York, NY 10029-6574
 Director: Tel: 212-241-6623
 FAX: 212-369-2344
 Information: 212-241-8329
 FAX: 212-996-0987

New York University

Steven H. Ferris, Ph.D.
 Aging and Dementia Research
 Center
 Department of Psychiatry
 (THN314)
 New York University
 Medical Center
 550 First Avenue
 New York, NY 10016
 Director: Tel: 212-263-5703
 FAX: 212-263-6991
 Information: 212-263-5700

University of Rochester

Paul D. Coleman, Ph.D.
Professor
Department of Neurobiology
and Anatomy, Box 603
University of Rochester
Medical Center
601 Elmwood Avenue
Rochester, NY 14642
Director: Tel: 716-275-2581
FAX: 716-273-1132
Information: 716-275-2581

NORTH CAROLINA**Duke University**

Allen D. Roses, M.D.
Director and Principal
Investigator
Joseph and Kathleen Bryan
Alzheimer's Disease Research
Center
2200 Main Street, Suite A-230
Durham, NC 27705
Director: Tel: 919-286-3228
FAX: 919-286-3406
Information: 919-286-3228
Clinic: 919-286-7299

OHIO**Case Western Reserve University**

Peter J. Whitehouse, M.D., Ph.D.
Director
Alzheimer's Disease Center
University Hospitals of Cleveland
11100 Euclid Avenue
Cleveland, OH 44106
Director: Tel: 216-844-7360
FAX: 216-844-7239

OREGON**Oregon Health Sciences
University**

Earl A. Zimmerman, M.D.
Chairman
Department of Neurology
(L-226)
Oregon Health Sciences
University
3181 SW Sam Jackson Park
Road
Portland, OR 97201-3098
Director: Tel: 503-494-7321
FAX: 503-494-7242
Information: 503-494-6976

PENNSYLVANIA**University of Pennsylvania**

John Q. Trojanowski, M.D., Ph.D.
Professor
Pathology and Laboratory
Medicine
University of Pennsylvania
School of Medicine
Room A009, Basement
Maloney/HUP
36th and Spruce Streets
Philadelphia, PA 19104-4283
Director: Tel: 215-662-6921
FAX: 215-349-5909
Information: 215-662-6920

University of Pittsburgh

Steven DeKosky, M.D.
Director
Alzheimer's Disease Research
Center
University of Pittsburgh
Medical Center
Montefiore University Hospital,
4 West
200 Lothrop Street
Pittsburgh, PA 15213
Director: Tel: 412-624-6889
FAX: 412-624-7814
Information: 412-692-2700

TEXAS**Baylor College of Medicine**

Stanley H. Appel, M.D.
Director
Alzheimer's Disease Research
Center
Department of Neurology
Baylor College of Medicine
6501 Fannin, NB302
Houston, TX 77030-3498
Director: Tel: 713-798-6660
FAX: 713-798-7434
Information: 713-798-6660

**University of Texas,
Southwestern Medical Center**

Roger N. Rosenberg, M.D.
Director
Alzheimer's Disease Research
Center
Zale Distinguished Chair and
Professor of Neurology and
Physiology
University of Texas
Southwestern Medical Center
at Dallas
5323 Harry Hines Boulevard
Dallas, TX 75235-9036
Director: Tel: 214-648-3239
FAX: 214-648-6824
Information: 214-648-3198

WASHINGTON**University of Washington**

George M. Martin, M.D.
Professor
Department of Pathology
Box 357470, HSB K-543
University of Washington
1959 NE Pacific Avenue
Seattle, WA 98195-7470
Director: Tel: 206-543-5088
FAX: 206-685-8356
Information: 206-543-6761

Alzheimer's Disease Education and Referral Center

The Alzheimer's Disease Education and Referral (ADEAR) Center provides information to health professionals, patients and their families, and the public. The ADEAR Center is a service of the National Institute on Aging (NIA), part of the Federal Government's National Institutes of Health.

ADEAR Center staff will:

- give you information about the latest research findings on Alzheimer's disease
- tell you about drug testing and studies of new treatments
- answer your questions about Alzheimer's disease
- suggest other groups to contact for more information and services
- send you publications about Alzheimer's disease and related disorders

Call the ADEAR Center's toll-free number, 800-438-4380, to talk with an information specialist. The Center is open from 8:30 a.m. to 5:00 p.m. EST, Monday-Friday. Our FAX number is: 301-495-3334. Our address is:

The ADEAR Center
PO Box 8250
Silver Spring, MD 20907-8250

Call 800-438-4380 or write to the ADEAR Center for these Alzheimer's disease publications:

FREE ☐ Activities for People with Alzheimer's Disease

List of publications about activities for people with Alzheimer's disease.

FREE ☐ Alzheimer's Disease Centers Program Directory (Z-01)

List of 28 national, NIA-funded Alzheimer's Disease Centers, which study the causes of and new treatments for Alzheimer's disease.

FREE ☐ Alzheimer's Disease Fact Sheet (Z-12)

Information about the symptoms of Alzheimer's disease, diagnosis, and treatment. Lists sources of more information.

FREE ☐ Recent Research on Alzheimer's Disease

Summary of current research on Alzheimer's disease.

*Social
Community
Resources*

7 pgs.

*Please ignore
cover sheet mis-
placed in Orange Box*

Community Resources

From:

Social Work and Alzheimer's Disease:
Effective Strategies for Assessment,
Counseling, and Referral

Elisabeth A. Hinman-Smith, M.S.W.

and

Lisa P. Gwyther, M.S.W.

Memory and Movement Disorders Clinic
Joseph and Kathleen Bryan Alzheimer's Disease Research Center (ADRC)
Division of Neurology, Department of Medicine
Duke University Medical Center
Durham, NC

Supported by an educational supplement grant (AG05128)
from the National Institute on Aging
1990

Note:

This information on community services is from a training manual for social workers, but it may be useful to other health professionals and families of Alzheimer's disease patients. Health professionals may purchase the manual in its entirety for \$6.00 payable to the Bryan ADRC. For more information, you may write to the Duke Family Support Program, Box 3600, Duke University Medical Center, Durham, NC 27710; or call 800-672-4213 (in North Carolina) or 919-660-7510. Reprinted by permission.

COMMUNITY RESOURCES

Social workers working with dementia patients and their families need to be aware of community services and when to refer families for formal help. Keep in mind that the availability of services is extremely variable from state to state and that services may have different names in different communities.

A description of some commonly available community resources and what they offer follows:

I. Support Services

- A. Meals on Wheels - This program delivers a hot noon meal to the home Monday through Friday. Costs vary widely, and there is usually some subsidy available. This service is supported by funds from the Older Americans Act and Social Services Block Grant. For the program nearest your client, contact the nearest Area Agency on Aging.

Example: Mr. B. is legally blind. Mrs. B.'s Alzheimer's disease has gradually erased her memory of how to cook. Mr. B. finds that home delivered meals have helped allow him and his wife to remain in their own home.

- B. Friendly Visiting - This program offers volunteers who stop by the home on a regular basis to write letters, shop or visit with an isolated elderly person. There is usually no charge for this service if it is run through churches or voluntary community groups. Start by contacting your client's church or an interfaith coalition for information.

Example: Mrs. S. has found caring for her demented sister to be isolating. Few of their friends come by, but through her church she was able to connect with a young volunteer who comes weekly to visit. Both Mrs. S. and her young visitor look forward to their time together.

- C. Telephone Reassurance - This program provides volunteers who make or receive daily phone calls from an elderly person living alone. Contact the nearest Area Agency on Aging.

Example: Mrs. O. lives alone and would like to continue to do so. Her son is concerned, but lives at a distance. Through a local telephone program, he knows she will be called every day.

IV. Home Health Care

- A. Home Health Care provides nursing services for maintaining or improving a person's health in his own home. Services can include skilled nursing care, physical therapy and speech therapy. Home Health Care may include personal care such as assistance with grooming or dressing provided by homemaker/home health aides. The costs can vary dramatically, depending on the service provided. It is best to call and compare public and private agencies. If the service is prescribed by a physician as "skilled", then Medicare will cover cost on a short-term basis. Some home health agencies are certified for Medicare and/or Medicaid and some are not. Some agencies will also accept private or work-related insurance. For this reason, it is very important to ask the agency what their rates are and whether they take third party payment.

Sources of Help: Try the local Health Department (for skilled care prescribed by MD). For a listing of private agencies in your area, consult the yellow pages.

- B. Medicaid Waiver Programs - One alternative for residents in some areas is Medicaid waiver community care. The goal is to postpone nursing home placement for Medicaid eligible older adults facing nursing home placement at the intermediate or skilled level of care. Check with your county Department of Social Services for more information.

Example: Mrs. S. wanted to keep her aunt in her home as long as possible, but could not afford to hire help, although her aunt needed a lot of personal care and supervision. The Medicaid Waiver Program in her county provided Mrs. S. with affordable help to bathe and care for her aunt and prolonged her time at home.

V. In-Home Respite Care

- A. In-home respite offers short-term temporary help to relieve caregiving family members of their responsibilities, allowing them to get away for as little as a couple of hours or as much as several days. In-home respite programs can be run through volunteer or paid sources (e.g. churches or home health agencies.) Costs incurred through a private agency are usually the same for "companion care" and are most often paid out-of-pocket. Some states subsidize respite programs and demonstration grants offer other sources of funding. Check with the state Division of Aging or your local Area Agency on Aging for more information.

Example: With the help of a trained respite worker, Mr. K. was able to play golf on Friday afternoons, an activity he had enjoyed for years. He knew his wife was in capable hands and that he would feel more rested when he got back home to her.

- D. Transportation Services - This program assists the elderly person in need of medical transport (doctor's visit, etc.), as well as shopping, socializing, group meals, or recreation. Call the nearest Area Agency on Aging.

Example: Mr. N. is not able to drive, but thanks to transportation services for the elderly, he never misses a doctor's appointment.

- E. Caregiver Support Groups - These groups are available in urban and suburban areas. They help meet information and support needs of Alzheimer's caregivers. For referral to a local support group, call the nearest chapter of the Alzheimer's Association or your Area Agency on Aging. Or, call the Alzheimer's Association at their national headquarters at 1-800-621-0379.

Example: Mr. L. found it difficult to discuss his feelings with his friends. His wife had always been his closest confidant, but now her Alzheimer's made it difficult for them to talk about anything, much less her illness. He took great comfort in attending monthly support groups in his town, where he came to know others experiencing similar problems and where he could learn more about managing her disease.

- II. Senior Centers (and Congregate Meals) - Senior Centers offer a variety of social, health, nutritional, educational and recreational services. A hot meal is served at noon and activities such as movies, crafts or guest speakers provide entertainment. Centers are usually open for several hours each day and meals are provided by donations based on the individual's ability to pay. No one is turned away. Some centers may provide free health checks and some offer transportation.

Example: Mrs. W. was still a very outgoing person, even though her memory had failed. She looked forward to going to the Senior Center nearby where she could eat lunch and socialize with friends each week.

- III. Chore Program - This program provides help in the home with laundry, housekeeping, cooking or shopping. It is usually run by the county Department of Social Services. Costs to participants vary, based on ability to pay. Unfortunately, because this is one of the most affordable services, it often has long waiting lists and strict financial eligibility.

Example: Mrs. G. spent most of her time caring for her demented husband at home. Always a good housekeeper, she really appreciated the few hours on Thursdays when the Chore worker would come to help with the housekeeping and laundry.

- VI. Out-of-Home Respite - Some nursing homes will offer short stays on a cost-per-day basis, at a maximum of 30 days. It is important to ask whether they will accept insurance coverage for these stays, though most do not.

Example: Mrs. L. was at a crisis point - she needed a rest from caring for her husband and also needed time to take care of unattended business. By arranging for a vacation respite stay for Mr. L., she was able to rest and then took time to make careful financial and legal decisions.

- VII. Adult Day Care - Day Care programs provide out of home scheduled activities, recreation, meals and exercise in a centralized place. Most centers are open Monday through Friday, during business hours. Participants can go as many days as they like, though often a minimum of two days is preferred, so that participants will become familiar with the group. Most programs also offer half day schedules. A hot meal is served at noon and usually morning and afternoon snacks are included. Some centers offer field trips and some will provide transportation to and from the center. Costs vary widely from \$15 per day to \$25, or more. Some centers specialize in working with dementia patients, but many require that participants be continent and ambulatory. An initial interview between the center director and the family/participant helps to determine the appropriateness of participation. Most centers operate on a private pay basis, though some reserve slots for Medicaid waiver patients. Centers may be operated by hospitals, nursing homes, local governments, religious groups or voluntary agencies.

Example: Mrs. J. found the adult day care program in her town to be a lifesaver. Her husband enjoyed the daily contact with others and she was able to keep working full-time.

- VIII. Adult Foster Care, Board and Care Homes or Domiciliary Care or Family Care Homes/Rest Homes - These homes go by a variety of names and can vary from state to state in the amount of care provided. They generally provide care for persons needing assistance in meeting day-to-day needs (ADL's). NO professional nursing or medical care is provided, but room and board, personal assistance, supervision of medications and social activities are. Family Care Homes are for six or fewer residents. Homes for the Aged are for more than six residents. Most of these homes are private pay, and quality and cost vary widely.

Example: Mrs. P.'s relatives all lived at a distance and she had no children. When Mrs. P. moved to a Family Care Home, she was delighted to be around other women with which she could share experiences. The family was relieved that she no longer had to cook or stay alone.

- XI. Hospice Care - This is a special type of care for the terminally ill. Hospice workers support both patient and family with physical, psychological, social and emotional care. Hospice can be provided in the home or in a hospice facility. Medicare covers hospice care, if ordered by a doctor. Hospice staff make a home assessment to determine the appropriate level of care and service needs.

Example: Mr. D. was determined to keep his wife at home, even through the last days of a long dementing illness. With the help of a local hospice organization and home nursing care, he was able to make her comfortable.

- XII. Intermediate Care Level - This care level is for those who don't need skilled care, but usually do need some nursing assistance and supervision. Individual treatment plans are drawn up and followed under the direction of an RN or an LPN supervised by an RN. Intermediate care provides a minimum of 8 hours a day licensed nursing supervision and 24-hour coverage by non-licensed personnel (Nurses aides). Costs range from roughly \$60 to \$80 per day. Medicare does not cover costs. Medicaid will cover cost, if prior approval is received and the facility is Medicaid certified. (In October 1990, the distinction between ICF and SNF will be dropped.)

Example: Mr. B. needed assistance with every activity of daily living. He could not bathe or dress himself, was incontinent of bowel and bladder and was developing problems with feeding himself. His wife was unable to care for him in their home and moved him to an intermediate care facility. She could visit him often and be sure he got the care he required.

- XIII. Skilled Nursing Care - This care level is for people who need intensive 24-hour care and supervision by a registered nurse under the direction of a doctor who is available for emergencies. A physician visits each patient at least once each month. Costs range from roughly \$90 to \$110 per day. Medicare, Medicaid and some private insurance policies will pay for this level of care under certain conditions.

Example: Mrs. R. wandered for much of the day due to her advanced stage of Alzheimer's disease. When she fell and broke her hip, she was placed on the Skilled Nursing Facility floor of the nursing home to receive more intensive medical care and physical therapy.

- IX. Congregate Housing - This housing is usually built with government financing (federal ,state or local) and is specifically designed for older or handicapped residents. Most congregate housing is rental and rent subsidies may be available through Supplemental Security Income, the Veterans Administration, or Section 8 Housing and Urban Development (HUD). Some congregate housing offers common dining areas, housekeeping and some personal care assistance. (Also known as "assisted living".)

Example: Mrs. E. wasn't doing well on her own, but could not move in with her daughter. When she moved into the congregate living facility, she was pleased to make some new friends and adapted well to the regular schedule of meals and activities.

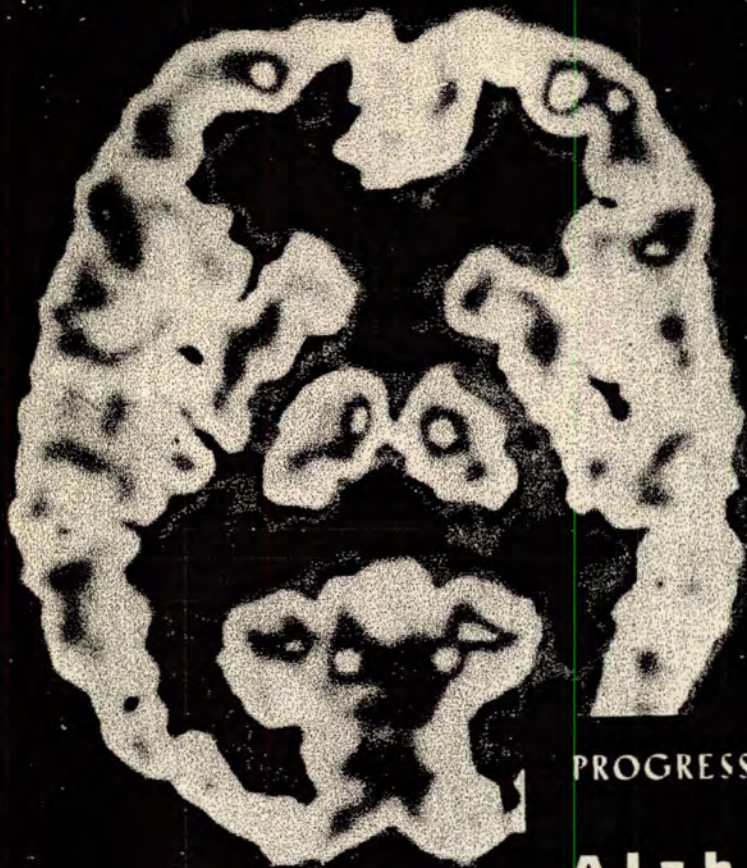
X. Retirement and Life Care Communities

- A. Retirement Communities or Villages - These communities are self-contained complexes that provide minimal services - usually recreation and security. Some provide dining rooms and health screenings. They may range from a multi-unit building, to a mobile home park to a housing development. These communities are private pay.

Example: Mrs. N. was concerned over her mother's memory loss. She moved her mother to a retirement community near the N. family home. Mrs. N. was pleased to see her mother participating in the field trips the community offered as she gradually made friends.

- B. Continuing or Life Care Communities - These are retirement communities offering a range of services, from independent living units to nursing home care. Residents usually pay a substantial entrance fee in addition to monthly payments for services included in the contract. They can move from one setting to another in the complex to obtain different levels of care but most require that residents move in at the independent level. These communities accept only private pay arrangements for residents at the independent level. If a resident advances to a skilled level of care and the skilled unit is Medicare or Medicaid certified, Medicare and Medicaid may cover the cost of some health services for a limited period.

Example: "The J.'s had moved to a continuing care community nearly four years ago. When Mr. J. began to develop symptoms of Alzheimer's disease, Mrs. J. was reassured by the knowledge that she could continue to care for her husband throughout his illness and not be forced to place him elsewhere. She also knew that if she fell ill, he would continue to be cared for".



PROGRESS REPORT ON

**Alzheimer's
Disease
1995**

National Institute on Aging
National Institutes of Health

Progress Report
on AD

29 pgs.

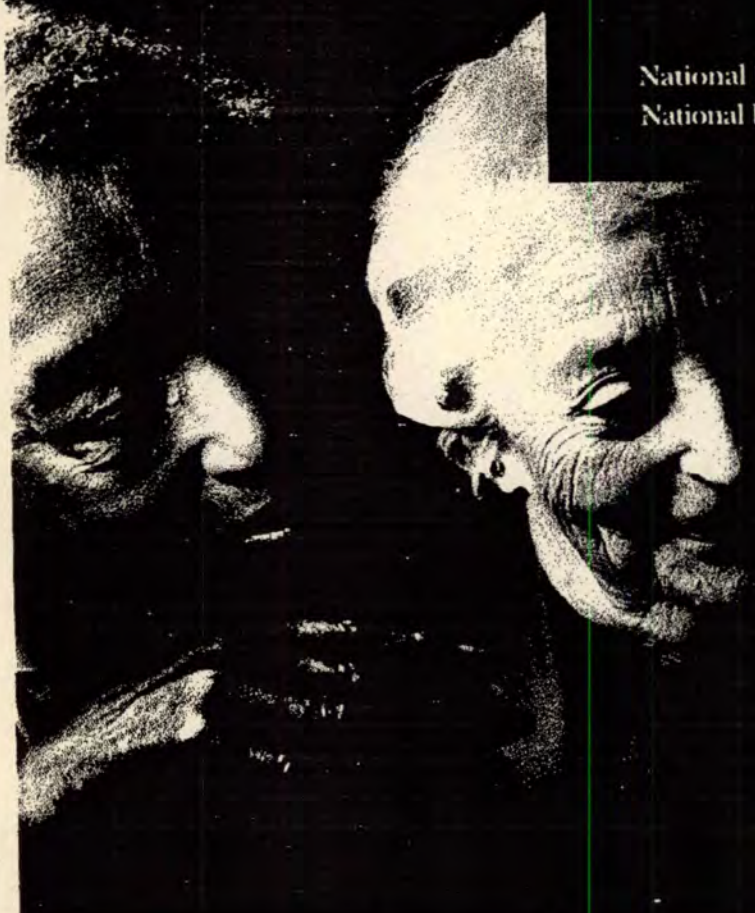
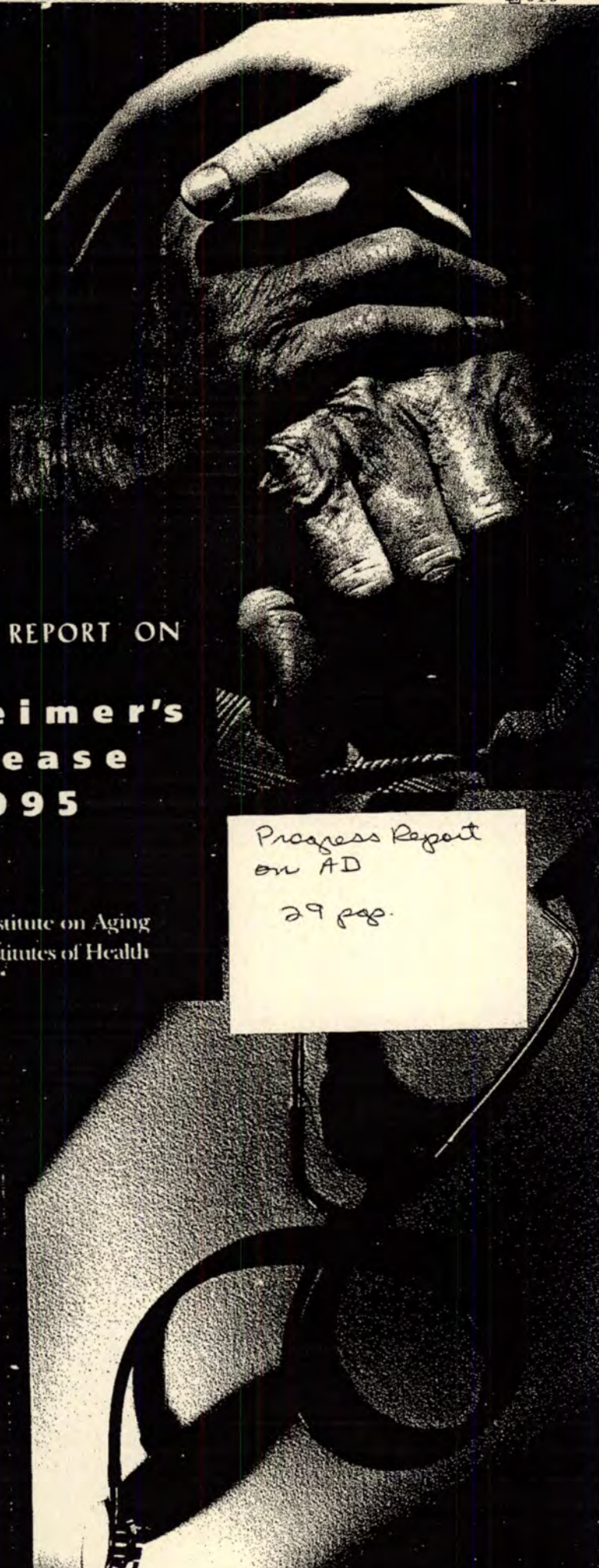


TABLE OF CONTENTS

ALZHEIMER'S DISEASE	2
Prevalence and Costs of Alzheimer's Disease	
Research Directions	
STRUCTURE AND FUNCTION OF THE BRAIN	4
CHANGES IN THE BRAIN IN ALZHEIMER'S DISEASE	5
Amyloid Plaques	
Neurofibrillary Tangles	
ADVANCES IN IDENTIFYING RISK FACTORS FOR ALZHEIMER'S DISEASE	8
The Link Between Alzheimer's Disease and ApoE	
Genes in Early-Onset Alzheimer's Disease	
Lower Educational and Occupational Levels Associated With Alzheimer's Disease	
Environmental Suspects	
ADVANCES IN DIAGNOSING ALZHEIMER'S DISEASE	14
Research on an Eye Test To Diagnose Alzheimer's Disease	
Changes in Immediate Visual Memory	
Predict Cognitive Impairment	
ADVANCES IN TREATING AND PREVENTING ALZHEIMER'S DISEASE	17
Inverse Association of Anti-Inflammatory Drugs and Alzheimer's Disease	
Estrogen	
Research on Dementia Special Care Units	
Alzheimer's Disease Centers Program	
RESEARCH CONDUCTED BY OTHER NIH INSTITUTES	21
National Institute of Diabetes and Digestive and Kidney Diseases	
National Institute of Neurological Disorders and Stroke	
National Institute of Arthritis and Musculoskeletal and Skin Diseases	
National Institute on Deafness and Other Communication Disorders	
National Institute of Mental Health	
National Center for Research Resources	
National Eye Institute	
National Institute of Allergy and Infectious Diseases	
OUTLOOK	28

ALZHEIMER'S DISEASE

Alzheimer's disease (AD) is the most common cause of dementia, or mental deterioration, among people age 65 and older. A slowly degenerative brain disease, AD is marked by changes in behavior and personality and by an irreversible decline in intellectual abilities. It impairs thinking, memory, and judgment, advancing in stages that range from mild forgetfulness to severe dementia. The course of the disease varies from person to person, as does the rate of decline. The average duration of AD is from 4 to 8 years.

People with this disease may forget how to do simple tasks, like brushing their teeth or combing their hair. Often, they are unable to think clearly or remember the right names of familiar objects or people. Eventually, they become completely dependent on others for their care.

Risk for AD increases with advancing age. After age 65, the percentage of people who suffer from AD or other dementias doubles with every decade of life. However, AD is *not* a part of normal aging. AD and other dementing disorders of old age are caused by specific diseases. Without disease, the human brain continues to function well, often into the tenth decade of life.

ALZHEIMER'S DISEASE

Prevalence and Costs of Alzheimer's Disease

Currently, an estimated 4 million Americans suffer from AD. In addition, the lives of countless caregivers are affected by this devastating illness. Families experience emotional, physical, and financial stress. They watch their loved ones become increasingly forgetful, agitated, and confused. Many caregivers, most of them women, juggle child care and jobs while caring at home for



A recent study estimated that the cost of caring for one person with AD is more than \$47,000 a year, whether the patient lives at home or in a nursing home.

relatives with AD who cannot function on their own. As the disease progresses and the abilities of people with AD steadily decline, family members face painful decisions about the long-term care of their loved ones.

Moreover, AD puts a heavy economic burden on society. A recent study estimated that the cost of caring for one person with AD is more than \$47,000 a year, whether the patient lives at home or in a nursing home. For a disease that can range in duration from 2 to 20 years, the overall costs of AD to families and to society are staggering.

Other factors in our changing society compound the problem of AD. Life expectancy has been increasing since the turn of the last century.

ALZHEIMER'S DISEASE

During the past three decades, improvements in public health measures, diet, and health behavior have brought about dramatic demographic changes, including a lower birthrate. Thus, today in most industrialized countries, the 85+ age group is the fastest growing segment of the population. The challenge of paying for health care for this population has yet to be tackled.

In light of these issues, AD, which primarily affects older people, represents a major health concern and expense for the United States. Until researchers find a way to cure or prevent AD, the number of people living to very old age (85+) and at risk for AD will continue to increase dramatically. Providing and financing the care of a growing older population present special challenges for our health care system.

Research Directions

AD research falls into three broad, overlapping areas of emphasis: cause(s)/risk factors, diagnosis, and treatment/caregiving. Research into the basic neurobiology of aging is critical to understanding what goes wrong in the brain affected by AD. Understanding the mechanisms by which nerve cells lose their ability to communicate with each other and the reasons for selective nerve cell death is at the heart of the worldwide scientific effort to discover the cause, or causes, of AD.

Epidemiology is an important research tool in determining risk factors and identifying potential interactions between genetic and non-genetic factors. Recent discoveries about the possible roles of inherited traits and education as risk factors for AD have taken researchers in new directions in their

ALZHEIMER'S DISEASE

search for answers. In addition, researchers are looking for better ways to diagnose and treat AD, improve a patient's ability to function, and support the caregivers of people with AD.

The National Institute on Aging (NIA) has primary responsibility for research aimed at finding ways to prevent, treat, and cure AD. This report highlights recent progress in AD research conducted or supported by the NIA and other components of the National Institutes of Health (NIH), including the:

- National Institute of Diabetes and Digestive and Kidney Diseases
- National Institute of Neurological Disorders and Stroke
- National Institute of Arthritis and Musculoskeletal and Skin Diseases
- National Institute on Deafness and Other Communication Disorders
- National Institute of Mental Health
- National Center for Research Resources
- National Eye Institute
- National Institute of Allergy and Infectious Diseases

Additional AD research projects, which are not summarized in this report, are supported by the: National Cancer Institute; National Heart, Lung, and Blood Institute; National Institute of Dental Research; National Institute of Child Health and Human Development; National Institute of Environmental Health Sciences; National Institute of Nursing Research; National Center for Human Genome Research; and Fogarty International Center.

STRUCTURE AND FUNCTION OF THE BRAIN

The brain integrates, regulates, and controls functions for the whole body, governing cognition, personality, and the senses. We are able to speak, move, and remember because of complex chemical processes that take place in the brain. The brain also regulates body functions that occur without our knowledge or direction, such as our heart rate and breathing.

The human brain is made up of billions of nerve cells, called neurons, which communicate with one another through a large array of biological and chemical signals. Even more numerous are glial cells, which surround, support, and nourish neurons. Each neuron has a cell body, an axon, and



Survival of nerve cells in the brain depends on the proper functioning of many interrelated systems that normally work in harmony.

dendrites. The nucleus within the cell body controls the cell's activities. The axon, which extends from the cell body, transmits messages to other neurons. Dendrites receive messages from axons of other nerve cells or from specialized sense organs.

Communications between neurons and other organs are transmitted through the synthesis and release of chemicals. When a nerve impulse reaches the end of the neuron, the signal triggers the

STRUCTURE AND FUNCTION OF THE BRAIN

release of neurotransmitters. These chemicals carry messages from the axons of nerve cells across the synapse (the gap between nerve cells) to the dendrites of other neurons. In this way, signals can travel back and forth across the brain in a fraction of a second. Millions of signals flash through the brain every moment.

Groups of neurons in the brain have certain jobs. For example, the cerebral cortex is a collection of neurons involved in thinking, learning, remembering, and planning.

Survival of nerve cells in the brain depends on the proper functioning of many interrelated systems that normally work in harmony. These systems control nerve cell activity related to communication, metabolism, and repair. The first system, communication between nerve cells, is described above. The loss or absence of any of several chemical messengers disrupts cell-to-cell communication and interferes with normal brain function.

The second system, metabolism, refers to the process whereby cells and molecules break down chemicals and nutrients into energy. Efficient metabolism in nerve cells depends on blood circulation to supply the cells with important nutrients, such as oxygen and glucose (a sugar). A sustained reduction in the supply of these nutrients can lead to nerve cell death.

The third system repairs and cleans up nerve cells. Unlike most other body cells, neurons live a long time. When neurons die, they cannot grow back or be replaced. Instead, living neurons constantly remodel themselves. Any disruption in cell cleanup and repair can have disastrous consequences for cell functioning. Research shows that the damage seen in AD is associated with changes in all three systems: nerve cell communication, metabolism, and repair.

CHANGES IN THE BRAIN IN ALZHEIMER'S DISEASE

In AD, the intricate process of communication between nerve cells breaks down. The destructive forces involved in AD ultimately cause nerve cell dysfunction, loss of connections between nerve cells, and death of some nerve cells. Death of neurons in key parts of the AD brain severely affects memory, cognition, and behavior.

AD destroys neurons in parts of the brain involved with cognition, especially the hippocampus (a structure deep in the brain that plays an important role in memory encoding). As the hippocampal nerve cells degenerate, short-term memory falters, and often, the ability to perform familiar tasks begins to decline as well. AD also attacks the cerebral cortex (the outer layer of the brain). The greatest damage occurs in areas of the cerebral cortex responsible for functions such as language and reasoning. Here, AD begins to take away language and change a person's judgment. Emotional outbursts and disturbing behaviors, such as wandering and agitation, appear with increasing frequency as the disease progresses.

In the final stages, AD wipes out the affected person's ability to recognize close family members or communicate in any way; the person becomes

CHANGES IN THE BRAIN IN ALZHEIMER'S DISEASE

totally dependent on others for care. People with AD often live for years, ultimately succumbing to a number of other diseases, but most often pneumonia.

Two abnormal structures are found in the AD brain: amyloid plaques and neurofibrillary tangles. Located outside and around neurons, plaques contain dense deposits of an amyloid protein and other associated proteins. Neurofibrillary tangles are twisted fibers inside neurons. Progress has been made in determining the makeup of amyloid plaques and neurofibrillary tangles and in proposing mechanisms that could account for their buildup in AD.

Amyloid Plaques

In AD, plaques develop in areas of the brain related to memory. These plaques consist of beta-amyloid mixed with dendritic debris from surrounding cells. Beta-amyloid is a protein fragment clipped from a larger protein (amyloid precursor protein) during metabolism. However, researchers do not know whether amyloid plaques cause AD or result from it.

CHANGES IN THE BRAIN
IN ALZHEIMER'S DISEASECHANGES IN THE BRAIN
IN ALZHEIMER'S DISEASE

Amyloid precursor protein (APP) is a member of a larger gene family of membrane proteins. During metabolism, APP pokes through the nerve cell membrane (wall), part inside the cell, part outside. Pausing there only briefly, it is replaced by new APP molecules being produced in the cell. While APP is embedded in the membrane, enzymes called proteases split APP in two. Only when the splitting occurs at a particular spot on APP is beta-amyloid the substance that is set free.

After the splitting, how the beta-amyloid segment moves through or around the nerve cells is less clear. However, in the final stages of its journey, it is known to join up with other beta-amyloid filaments and fragments of dead and dying dendrites. Together, these form the dense and insoluble plaques that characterize AD.

Large numbers of beta-amyloid deposits in the brain can occur in older humans and some other mammals without surrounding nerve cell changes. This finding suggests that beta-amyloid initiates and/or is only an early disordered product in a slow, multi-step process that ultimately leads to brain cell malfunction.

Several studies have centered on how beta-amyloid is processed and how APP is broken down by enzymes. Other investigations are seeking clues in beta-amyloid's environment. For example, substances near beta-amyloid may bind to it normally and thus keep it in solution. But in AD, according to one theory, something causes the beta-amyloid to drop out of solution and form insoluble plaques. Another candidate for the role of keeping beta-amyloid in solution is a form of a protein called apolipoprotein E (ApoE).

Other areas of research center on how beta-amyloid affects neurons. In one laboratory study, hippocampal neurons died when beta-amyloid was added to the cell culture, suggesting that the protein is toxic to neurons. Results of another recent study suggest that beta-amyloid breaks into fragments, releasing free radicals that attack neurons. Free radicals are unstable molecules that can do damage in the body. In AD, a buildup of oxygen free radicals, leading to the breakdown of nerve cell membranes, is thought to play a role in cell death.

The precise mechanism by which beta-amyloid may cause nerve cell death is a mystery. However, one recent finding suggests that beta-amyloid forms small channels in neuron membranes. These channels may allow excess amounts of calcium to enter the nerve cell, which is a lethal event.

Other recent studies indicate that beta-amyloid disrupts potassium channels, which also could affect calcium levels. Yet another study links beta-amyloid to reduced choline levels in nerve cells.

CHANGES IN THE BRAIN IN ALZHEIMER'S DISEASE

Since choline is an essential component of acetylcholine, a neurotransmitter, this finding suggests a link between beta-amyloid and acetylcholine.

Beta-amyloid is not the only protein implicated in AD. Not long after the discovery of beta-amyloid, scientists found the protein that is the principal component of neurofibrillary tangles, the other hallmark of AD.

Neurofibrillary Tangles

Neurofibrillary tangles are abnormal collections of twisted threads found inside nerve cell bodies. They are the remains of the neuron's microtubules, the cell's internal support structures. The chief component of tangles is a protein called A68, a form of *tau*.

In healthy neurons, microtubules are formed like train tracks, long parallel rails with cross-pieces, that guide nutrients from the bodies of the cells down the ends of the axons. In cells affected by AD, these structures collapse. *Tau* normally forms the crosspieces of the microtubules, but in AD it twists into paired helical filaments, two threads wound around each other. These paired helical filaments are the major component of neurofibrillary tangles. No one has discovered yet why the microtubules collapse, but according to one theory, it may be due to the presence of a gene product called ApoE4.

The collapse of nerve cell supports may result in the breakdown of communication between nerve cells and finally cause neurons to die. Still unknown, however, is whether abnormal processing causes *tau* to come away from the nerve cell

CHANGES IN THE BRAIN IN ALZHEIMER'S DISEASE

supports or whether abnormal processing is the result of *tau* being gathered into the paired helical filaments. In addition, abnormal *tau* processing may simply indicate problems with metabolism of other, as yet unknown, nerve cell proteins. Sustained triggering of a single enzyme may disrupt other normal body functions that affect the survival of brain cells. To determine why some nerve cells are vulnerable to AD and others are not, researchers first must understand the causes of abnormal processing and the regulation of certain enzymes.



In healthy neurons, microtubules are formed like train tracks, long parallel rails with cross-pieces, that guide nutrients.... In cells affected by AD, these structures collapse.

Scientists may be able to develop animal models using mice that produce excess enzymes involved in *tau* processing. Further clues may lie in recent research using "knockout" mice (mice in which the regulation of an enzyme that helps process *tau* is altered). These and other routes could lead to an animal model for use in testing drugs to reverse or limit early brain cell damage caused by AD.

ADVANCES IN IDENTIFYING RISK FACTORS FOR ALZHEIMER'S DISEASE

Although healthy aging does not result in dementia or AD, aging remains the most strongly associated risk factor for AD. Family history is another important risk factor. A history of AD in a parent or sibling increases the odds of developing AD by three to four times. Researchers believe that genetic (inherited) factors may be involved in more than half of the cases of AD. In addition, a severe head injury that leads to a brief loss of consciousness doubles the risk of developing AD later in life. These three risk factors—age, family history, and head injury—meet the accepted epidemiologic criteria for causal factors: they provide a plausible biological explanation, and their effects are strong and consistent.

Other risk factors that do not meet the above criteria have been studied, including exposure to environmental toxins (such as aluminum) or to chemicals (such as benzene and toluene). The detection of aluminum, zinc, and other metals in the brain tissue of people with AD is being studied to see whether such deposits influence the disease process or whether they are the results of disrupted brain structures. In addition, gender may play a role in the disease. Further research

ADVANCES IN IDENTIFYING RISK FACTORS FOR ALZHEIMER'S DISEASE

is needed to confirm recent data showing higher rates of AD among women. This finding may only reflect the effects of age, since women live longer, on average, than men.

It is becoming clear that the cause of AD is not a single factor, but a host of factors that interact differently in different people. In most cases, genetic factors alone are not enough to bring on AD. Genetic indicators have been found in some patients with the disease and in their relatives who do not yet show signs of impairment. Other risk factors may combine with a person's genetic make-up to increase the chances of developing AD.



It is becoming clear that the cause of AD is not a single factor, but a host of factors that interact differently in different people.

Researchers studying the incidence and prevalence of AD and related dementias in later life seek to identify specific risk factors for AD and to show how and why AD develops. Incidence refers to the rate at which new cases of a disease occur. Prevalence is the percentage of the entire population with the disease at a given time. By studying people in different ethnic, racial, and social groups, scientists may discover additional risk factors for AD. These risk factors, in turn, may suggest new theories that can be tested regarding the disease's origin.

ADVANCES IN IDENTIFYING RISK FACTORS FOR ALZHEIMER'S DISEASE

In the past year, researchers have examined risk factors that may speed up or slow down the onset of AD and increase or decrease a person's risk of AD. They focused on determining whether ApoE, education and occupation levels, a gene on chromosome 14, or zinc, aluminum, and other metals are related to AD. Their findings eventually may lead to treatment and prevention strategies.

The Link Between Alzheimer's Disease and ApoE

A gene is the biologic unit of heredity that has a precise location on a chromosome. Chromosomes are structures in the nucleus of cells that transmit hereditary information using a molecule called deoxyribonucleic acid (DNA). Genes direct the manufacture of every enzyme, hormone, growth factor, and other protein in the body. They help determine a person's traits, for example, what he or she looks like. Genes are made up of four chemicals, or bases, arranged in various patterns within the DNA. Each gene has a different sequence of bases, and each one directs the manufacture of a different protein. Even slight alterations in the DNA code of a gene can produce a faulty protein. And a faulty protein can lead to cell malfunction and eventually disease.

Genetic research has turned up evidence of three gene alterations that are more common in AD patients than in the general population. One, the ApoE4 gene on chromosome 19, has been linked to the most common form of AD, called late-onset AD, which appears in older people.

ADVANCES IN IDENTIFYING RISK FACTORS FOR ALZHEIMER'S DISEASE

Researchers also have found genes on chromosomes 14 and 21 that are more common among people who develop AD earlier, in middle age.

Everyone has ApoE, which helps transport cholesterol in the blood throughout the body. The gene for ApoE occurs in three versions: ApoE2, ApoE3, and ApoE4. Every person inherits two ApoE genes, one from each parent. Scientists are studying people with different versions of this gene. ApoE3 is the most common one found in the general population. However, ApoE4 occurs in about two-thirds of all late-onset AD patients and is not limited to people with a family history of AD.

Collaborating researchers at the Duke University General Clinical Research Center and the Joseph and Kathleen Bryan Alzheimer's Disease Research Center in Durham, North Carolina, studied the relationship between ApoE4 and AD. Their research was supported by the NIA and the National Center for Research Resources (NCRR). These scientists found that the risk for AD in people with the gene for ApoE4 is three times greater than that for other people. For example, a 78-year-old person with two copies of the gene for ApoE4 has a 98 percent chance of having the disease, with one copy a 60 percent chance, and with no copies a 25 percent chance.

ADVANCES IN IDENTIFYING RISK FACTORS FOR ALZHEIMER'S DISEASE

In addition, this research shows that the presence of ApoE4 also lowers the age of onset of AD. On average, people with two copies of the gene for ApoE4 start showing AD symptoms before age 70 and are eight times more likely to develop AD than those who have two copies of the more common ApoE3 version. For those with no copies of ApoE4, the average age of onset is older than 85 years. According to these scientists, AD risk increased because the age of onset decreased. In some unknown way, ApoE4 may speed up the AD process.

These researchers also found that ApoE is localized in the senile plaques and neurofibrillary tangles found in AD. Moreover, Duke University researchers now believe that ApoE is located in all neurons in both healthy and AD brains.

Researchers at the Mayo Clinic in Rochester, Minnesota, followed 71 older patients with mild memory impairment. Almost half had clinical dementia after 3 years. Over two-thirds of those with clinical dementia with a copy of the gene for ApoE4 continued to decline, and ApoE4 best predicted who would decline. ApoE4 appears to mark susceptibility to AD. However, the presence of ApoE4 in a blood sample does not predict AD. A person can have ApoE4 and not get the disease, and a person can get AD without having ApoE4.

ADVANCES IN IDENTIFYING RISK FACTORS FOR ALZHEIMER'S DISEASE

The relatively rare protein ApoE2 may protect people against the disease; it seems to lower the risk for AD and increase the age of onset. For instance, people with one ApoE2 gene and one ApoE3 gene have only one-fourth the risk of developing AD as people with two ApoE3 genes.

Some researchers supported by the NIA and NCRR exploring the function of the protein product of ApoE4 point to beta-amyloid. While the ApoE4 protein binds rapidly and tightly to beta-amyloid, the ApoE3 protein does not. Normally, beta-amyloid is soluble, but when the ApoE4 protein latches on to it, the amyloid becomes insoluble. This may mean that it is more likely to be deposited in plaques. Studies of brain tissue suggest that ApoE4 increases deposits of beta-amyloid and that it directly regulates APP.

Other researchers believe that the presence of ApoE in neurons may affect certain cell processes and how synapses function. Also, scientists conducting test tube studies found marked differences in the rates at which ApoE3 and ApoE4 bind to *tau* protein and to a similar protein found in dendrites. One hypothesis suggests that the ApoE4 product allows the microtubule structure to come undone in some way, leading to the neurofibrillary tangles.

While still controversial and far from proven, the hypotheses surrounding ApoE4 are driving new research. One next step is to see how *tau* and beta-amyloid react with ApoE in its several forms in living

ADVANCES IN IDENTIFYING RISK FACTORS FOR ALZHEIMER'S DISEASE

cells. Other experiments will be designed to determine the actions and role of ApoE. Once these are clear, it should be easier to understand how ApoE's function might be affected by drugs. For instance, if ApoE2 turns out to be beneficial, then substances that mimic its effects might be developed to help slow or prevent the progress of AD.

Theories surrounding ApoE4 are not confined to the proteins. Its effect on dendrites intrigues some scientists, because of findings that dendrites in patients with the ApoE4 gene are shorter, pruned



The relatively rare protein ApoE2 may protect people against the disease; it seems to lower the risk for AD and increase the age of onset.

back apparently by some unknown agent. The result may be that, compared to normal dendrites, these pruned dendrites cannot form as many connections with other nerve cells. Although this pruning also can occur in people without the ApoE4 gene, it happens 20 to 30 years earlier in people with ApoE4.

In addition, environmental factors may interact with genetic factors. Researchers at the Neurological Institute in New York City believe that repeated head injuries do not increase the risk of developing AD without ApoE4. However, when ApoE4 is present, these scientists found that repeated head injuries increase risk for AD by 10 times.

ADVANCES IN IDENTIFYING RISK FACTORS FOR ALZHEIMER'S DISEASE

With ApoE, scientists have a biological indicator for AD for the first time. ApoE can be used to sort populations and follow the subgroups with the hope of finding other risk factors. Scientists still must learn how ApoE and its various genes function in the brain and relate to other risk factors for AD. Larger population-based studies are needed to clarify the link between ApoE4 and AD, and to confirm the protective effect of ApoE2. Further explanation of preliminary findings may lead to ways to reduce the effects of ApoE4, develop drugs to treat or prevent AD, and ultimately, decrease the occurrence of AD. Moreover, some scientists suggest that testing for the ApoE4 gene someday may help in the diagnosis of AD.

Genes in Early-Onset Alzheimer's Disease

AD can strike early and often in some families—often enough to be singled out as a separate form of the disease, called early-onset familial AD (FAD). Combing through the DNA of some of these early-onset FAD families, researchers at St. Mary's Hospital Medical School in London, England, previously found an abnormality in one gene on chromosome 21 that is common to a few of the families. And they have mapped another gene, which occurs in a much larger portion of early-onset families, to a region on chromosome 14.

The gene on chromosome 21 carries the code for an abnormal form of APP, the parent protein for beta-amyloid. The discovery of this gene supports the theory that beta-amyloid plays a central

ADVANCES IN IDENTIFYING RISK FACTORS FOR ALZHEIMER'S DISEASE

role in some forms of AD, although it has been found only in about 5 percent of early-onset FAD families. In addition, the gene on chromosome 21 is the gene involved in Down syndrome. Down syndrome is similar to AD in one respect. People with Down syndrome have an extra version of chromosome 21, and, as they grow older, usually develop plaques and tangles like those found in AD.

Compared to the chromosome 21 gene, the gene on chromosome 14 occurs more often in people with FAD. However, so far, no one knows exactly what gene it is. The gene has been tracked to a specific region on chromosome 14. Scientists at the University of Washington in Seattle still are trying to find the gene among the 10,000 or so DNA bases in this region.

Lower Educational and Occupational Levels Associated With Alzheimer's Disease

Scientists at Columbia University in New York City have established a relationship between increased risk for AD and lower educational and occupational levels. The researchers found that people with either lower educational or occupational levels have at least twice the risk for developing AD, compared to those who have had 6 to 8 or more years of schooling. The risk is three times greater when low occupation and low education occur together.

ADVANCES IN IDENTIFYING RISK FACTORS FOR ALZHEIMER'S DISEASE

For 4 years, researchers administered yearly neuropsychologic tests to 593 people age 60 and older to see if any of them began to show signs of dementia. The results were analyzed based on educational level (kindergarten through college) and occupational level. A low level of education was set at 8 years of schooling, and occupational levels were based on U.S. Census categories. At the study's end, over 25 percent of the participants showed some sign of dementia.

These researchers do not know why low occupation and education are linked with AD. They believe that higher occupational and educational backgrounds may allow people to cope better with the effects of AD for a longer time before symptoms occur. People with more education may develop a protective reserve of brain cells or synapses. Also, increased mental capacity may allow these people to find additional ways to do daily activities. Or, education may be related to another factor, such as socioeconomic or nutritional status, which may be the reason for increased risk.

This study adds information about psychosocial factors related to AD. Investigators and caregivers now have another factor to consider when evaluating whether failing memory and confusion are signs of AD or some other, possibly treatable, problem. If some aspects of life experience can delay the onset of AD for even a short time, the overall prevalence and costs of the disease will be reduced significantly. This also could enhance the quality of life for many people.

ADVANCES IN IDENTIFYING RISK FACTORS FOR ALZHEIMER'S DISEASE

Environmental Suspects

Certain environmental factors, such as metals and poisons carried in foods, may play a role in the development of AD. The most studied of these factors are aluminum and zinc. Researchers continue to study whether some metals are related to the development of disease markers such as plaques and tangles in brain tissue of AD patients. To date, no conclusive evidence links metals such as aluminum or zinc to AD.

One of the most publicized and controversial hypotheses in AD research concerns aluminum. This aluminum theory goes back to the 1970's, when researchers found traces of aluminum in the brains of AD patients. Many studies since then either have not been able to confirm this finding or have produced questionable results.

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

Other studies have shown that groups of people exposed to unusually high levels of aluminum have no increased risk of AD. Moreover, aluminum in cooking utensils does not get into food, and the aluminum that does occur naturally in some foods, such as potatoes, is not absorbed well by the body. On the whole, most scientists now believe that there is little chance that exposure to aluminum causes AD.

ADVANCES IN IDENTIFYING RISK FACTORS FOR ALZHEIMER'S DISEASE

Zinc has been implicated in AD in two ways, some reports suggesting that too little zinc is a problem, others that too much zinc is at fault. Too little zinc was suggested by autopsies that found low levels of zinc in the brains of AD patients, especially in the hippocampus. There is some evidence that zinc deficiency can add to the symptoms of AD.



To date, no conclusive evidence links metals such as aluminum or zinc to AD.

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

ADVANCES IN DIAGNOSING ALZHEIMER'S DISEASE

A definitive diagnosis of AD is based on the presence of plaques and tangles in the brain. Plaques and tangles can be found only by examining brain tissue (a brain biopsy), and this procedure usually is done only as part of an autopsy.

Currently, no definitive test exists to diagnose AD. However, a probable diagnosis of AD can be made based on the patient's medical history, a physical examination, and tests of mental ability. Several other conditions, some of which are treatable, also may cause memory or other cognitive deficits and must be ruled out. These include thyroid gland problems, drug reactions, depression, brain tumors, and dementia caused by blood vessel disease in the brain.

A patient history includes a review of present and past medical problems, as well as an examination of current ability to carry out daily activities. Clinical analyses used to decide whether a person has AD or another disease include tests of blood and urine samples and an examination of a small sample of cerebrospinal fluid.

Neuropsychological tests are used to evaluate a person's mental abilities in many areas, including memory, problem solving, attention, calculation, and language. Brain imaging also may be used to detect abnormalities in the brain. The results of

ADVANCES IN DIAGNOSING ALZHEIMER'S DISEASE

all tests and the patient's medical history help the doctor determine if symptoms are caused by AD or by another condition.

Early and accurate diagnosis of AD has a major effect on the progress of research on dementia and is of utmost concern to patients and their families. Although the early and accurate diagnosis of AD is difficult, a reliable diagnosis with 80 to 90 percent accuracy (when compared to autopsy findings) can be obtained in many specialized centers.

Improving the diagnosis of AD using various procedures would allow patients and their families to know what stage of the illness they are dealing with and help them plan for the future. It also



Although early and accurate diagnosis of AD is difficult, a reliable diagnosis with 80 to 90 percent accuracy (when compared to autopsy findings) can be obtained in many specialized centers.

would improve the planning and design of drug trials, because drugs may work more effectively to alter the course of the disease in patients with early-stage AD. These methods would help identify patients early in the course of the illness when they have experienced the smallest degree of nerve cell damage and cognitive loss. The earlier and more accurate the diagnosis, the greater the gain in managing the clinical course of the illness, determining its natural history, and providing information about its causes and treatment.

ADVANCES IN DIAGNOSING ALZHEIMER'S DISEASE

The NIA supports research to identify dementia indicators; develop tests and methods related to differential diagnosis, screening, etiology (the study of the causes of the disease), risk factors, and family history; improve research designs; and refine diagnostic criteria.

One goal of current research is to develop an accurate test for AD. The search continues for a biological indicator that can identify AD cases very early in the course of the disease, when treatment still could be effective. Neuropsychologic tests are needed that pinpoint the stages of AD. These tests would separate people who are in the earliest stages of AD from people who have cognitive deficits that are related to healthy aging. Brief cognitive screening tools are proliferating. However, the relationship of the results of one test to another, to careful clinical diagnosis of abnormalities, and ultimately to brain cell death remains unknown.

Experimental technology for imaging the brain continues to develop rapidly. New procedures include positron emission tomography (PET), single photon emission computed tomography (SPECT), magnetic resonance imaging (MRI), and magnetic resonance spectroscopy imaging (MRSI). MRI provides high-resolution images of the brain. MRSI allows observation of various metabolites in the brain without the use of radioactive tracers. Metabolites are substances that are produced when energy is made available for cell use. Scientists are working to learn how metabolites change with aging and with AD and how to relate these changes to cognitive impairment. MRSI may offer a way to establish early diagnosis, determine prognosis, monitor patients, and evaluate treatment efficacy.

ADVANCES IN DIAGNOSING ALZHEIMER'S DISEASE

Researchers have yet to understand the relationship between the results of various brain imaging methods and the person's clinical condition. In addition, methods used to analyze imaging results need to be standardized. In the future, researchers hope to put information from imaging techniques that evaluate structure and those that analyze function together into a unified diagnostic summary.

Research on an Eye Test To Diagnose Alzheimer's Disease

Researchers at the Harvard Medical School in Boston, Massachusetts, are working on developing a simple eye test for detecting the presence of AD. Eventually this test may help diagnose patients with AD. Preliminary results suggest that monitoring pupil dilation (expansion) after exposure to certain eye drops may one day be the basis of an easy, accurate way to diagnose AD.

Data in this study suggest that the pupils of healthy people or those with non-AD dementia dilated about 5 percent after receiving the eye drops. The pupils of people with AD dilated 23 percent. This test pointed to AD in 18 of 19 people believed to have AD. Furthermore, pupils seemed to be sensitive to the chemical very early in the course of the disease, when emerging treatments are likely to be most effective. This test now must be studied in many more people to determine whether it holds up in different types of people with different types of AD, and distinguishes AD from other neurologic illnesses.

ADVANCES IN DIAGNOSING ALZHEIMER'S DISEASE

Changes in Immediate Visual Memory Predict Cognitive Impairment

NIA researchers have found that changes occurring over 6 years in immediate visual memory performance, assessed by the Benton Visual Retention Test (BVRT), predict AD before the onset of cognitive symptoms. Immediate visual memory refers to the ability to remember and name, within seconds, things seen. The BVRT requires subjects to reproduce geometric designs from memory after studying them for 10 seconds. Each test consists of 10 separate designs with 1 or more figures, and the score is the total number of errors made in reproducing the designs.

Researchers in the NIA's Baltimore Longitudinal Study of Aging examined data for 254 men and 117 women, who were administered cognitive, neuropsychologic, and neurologic tests between 1986 and 1992. These people were generally healthy and ranged in age from 55 to 95 at the initial testing. Six of them had probable AD, and one had definite AD.

ADVANCES IN DIAGNOSING ALZHEIMER'S DISEASE

Compared to those without AD, subjects with the disease had larger changes in the numbers of errors in immediate memory performance over the 6 years prior to the onset of AD. This finding implies that AD may be identified by changes in memory performance sooner than other changes can be detected by clinical evaluation. Six-year change in immediate visual memory performance also predicted cognitive performance from 6 to 15 years and from 16 to 22 years later. This was true even after adjusting for the influences of age, general ability, and initial immediate memory.

In addition, these results suggest that change in recent memory performance, a critical component in diagnosing AD, may be an important precursor of the development of the disease. Recent memory performance generally refers to recall after a short delay, such as 20 minutes.

The results show the value of longitudinal studies because predictions of risk for subsequent disease are possible only when baseline and followup data are gathered before the onset of disease. This is particularly important for AD, because little is known about the earliest stages of AD. However, this period is likely to be when the disease is most responsive to treatment.

ADVANCES IN TREATING AND PREVENTING ALZHEIMER'S DISEASE

There currently is no effective way to treat or prevent AD. However, several substances are being tested to see if they can slow or reverse the decline in those behavioral and cognitive skills that are impaired by AD.

Pharmacologic and behavioral treatments for the non-cognitive behavioral symptoms related to AD also are being studied. These symptoms include aggression, agitation, wandering, depression, sleep disturbances, and delusions.

The drug tacrine (also known as THA or Cognex) may temporarily slow the rate of decline in memory and thinking ability in some patients who are in the mild and moderate stages of the disease. Experimental drug treatments may be available to AD patients through clinical trials conducted at large teaching hospitals and universities. Several of these experimental drugs have shown promise in easing symptoms in some patients.

Moreover, medications may help control behavioral symptoms, thereby making some patients more comfortable and making their care easier for caregivers. For example, several drugs now in use may improve sleep patterns, reduce agitation and wandering, or ease anxiety and depression.

Scientists studying drug and non-drug treatments seek to reduce disruptive behaviors, allow patients to live in the least restrictive manner possible while maximizing their dignity and independence, reduce caregiver stress, and keep or re-establish patients' self-care abilities. In addition, effective treatments would decrease significantly the economic costs to families and society by reducing the need to institutionalize

ADVANCES IN TREATING AND PREVENTING ALZHEIMER'S DISEASE

patients. Overall, these research efforts are designed to increase the intellectual, emotional, and social well-being of patients, families, and caregivers.

In 1994, the NIA funded a 5-year study to screen for potential toxic effects of new drugs to treat AD. The data gathered will be used to file Investigational New Drug requests with the Food and Drug Administration so that compounds can be taken quickly from animal testing into human clinical trials.

Thirty-five sites in the Alzheimer's Disease Cooperative Study Unit (ADCSU) are located primarily at the Alzheimer's Disease Research Centers and Alzheimer's Disease Core Centers. The ADCSU is conducting trials of deprenyl and vitamin E, drugs used to treat agitation, an anti-inflammatory agent, and estrogen. In addition, the ADCSU is testing neuropsychologic instruments in the areas of cognitive change, behavioral change, global assessment, and activities of daily living. The ADCSU also is adapting instruments for use with people who are severely impaired and with those who do not speak English. Future ADCSU work will involve designing trials to evaluate whether a substance can prevent AD.

In addition, postmenopausal estrogen replacement therapy, long-term use of anti-inflammatory drugs, and cigarette smoking have been implicated as having a protective effect against AD. These all need to be confirmed by further and more careful studies.

ADVANCES IN TREATING AND PREVENTING ALZHEIMER'S DISEASE

Inverse Association of Anti-Inflammatory Drugs and Alzheimer's Disease

Anti-inflammatory drugs are used to ease symptoms of arthritis or related conditions. Recently, they have been proposed as a means of slowing the progression of AD symptoms. Studies of twins suggest that the use of anti-inflammatory agents may relate to the etiology and prevention of AD.

NIA-funded researchers at the Duke University Medical Center and Johns Hopkins University School of Hygiene and Public Health studied 50 sets of older twins with AD. They found a lower incidence of AD among those who had used anti-inflammatory drugs to treat arthritis. These findings suggest that inflammatory mechanisms may be involved in the development of AD. They also indicate that anti-inflammatory agents may prevent or delay the onset of AD symptoms.

Estrogen

Preliminary data from previous animal and human studies suggest that estrogen may protect older women against AD. However, recent research has generated some conflicting results. Initial results from one study by researchers at the University of Washington, Seattle, provide no evidence that post-menopausal estrogen replacement therapy influenced the risk of AD in women. Using computerized pharmacy data, these researchers compared the use of estrogen replacement therapy

ADVANCES IN TREATING AND PREVENTING ALZHEIMER'S DISEASE

by 107 women with AD and 120 women without AD. Estrogen use was not associated with AD.

Other NIA-funded researchers at the University of Southern California School of Medicine, Los Angeles, analyzed data for 138 older women who had died and whose death certificates listed AD or related dementias. Their results suggest that risk of AD and related dementia was lower in estrogen users than in non-users. Risk of AD decreased significantly with increasing estrogen dose and with increasing duration of estrogen use. Risk of AD also was associated with variables related to estrogen levels produced naturally in women. Data also suggest that risk of AD increased with increasing age at the onset of menstruation and decreased with increasing weight.

Overall, this study suggests that the increased incidence of AD in older women who have undergone menopause may be due to estrogen deficiency. Further research is needed to determine whether estrogen replacement therapy can slow down AD-related nerve cell death, and delay the onset of AD or prevent it altogether. Additional research will allow scientists to analyze how and why these and other studies have conflicting results.

Research on Dementia Special Care Units

Another line of AD research sponsored by the NIA concerns the effectiveness of special care units (SCU's) across the Nation. The results of these studies may provide ways to improve care for patients with AD and related dementias.

Dementia SCU's are long-term care settings designed to meet the needs of people with AD and related mental impairments. SCU's emerged

ADVANCES IN TREATING AND PREVENTING ALZHEIMER'S DISEASE

in the 1980's as a care option for patients with AD. Forces creating a demand for specialized care include the growing numbers of older people; the recognition that the care needs of people with dementia differ from those of physically frail people; and the widespread concern that standard nursing home care has been unresponsive to the special needs of people with AD and related disorders, their families, and caregivers.



...of the Nation's 15,555 licensed nursing homes, 9.6 percent had dementia Special Care Units, with an estimated capacity of about 47,878 residents.

Since their beginnings, SCU's have proliferated rapidly and grown in diversity. The 1990-91 National Survey of Special Care Units in Nursing Homes found that of the Nation's 15,555 licensed nursing homes, 9.6 percent (1,497 nursing homes) had SCU's, with an estimated capacity of about 47,878 residents. While most nursing homes with SCU's presented some features considered important for SCU's, only 647 met all of them. Projections from this survey suggest that 16.7 percent of all nursing homes will offer SCU's in 1995.

To explore the effectiveness of SCU's, the NIA funded a 5-year multi-center Special Care Unit Initiative, beginning in 1991. Under this program, the NIA financed 10 research projects to examine SCU's throughout the United States.

ADVANCES IN TREATING AND PREVENTING ALZHEIMER'S DISEASE

Several research issues have emerged since 1991. There is a lack of standardization about what constitutes an SCU versus a non-SCU. Use of uniform descriptive data is critical because SCU's vary in size, age of patients, and whether or not patients are segregated from the general nursing home population. SCU's also can differ in how they recruit residents for participation in studies. Research studies need to establish the diagnosis and cognitive level of residents to identify a sample group for study.

The proliferation of SCU's means that for the first time in the United States, administrators and staff members in numerous nursing homes are developing methods of care specifically for their residents with dementia. Better methods of care cannot be realized without formal research to describe, compare, and evaluate the various methods being used. There still is a need for more research on classification, design characteristics, costs, and effectiveness of SCU's. For public policy purposes, the most important research questions pertain to the effectiveness of SCU's for their residents, the residents' families, and the unit staff members; and the impact of SCU's on residents with and without dementia in non-specialized nursing home units.

Further research will provide a better idea of what constitutes "special care" and identify which features of SCU's are most important in terms of environment, staffing, activities, care planning, admission policies, size, and patient segregation.

ADVANCES IN TREATING AND PREVENTING ALZHEIMER'S DISEASE

Additional studies will determine whether effective SCU's cost more than traditional nursing home units. Eventually, the results of these studies will enable caregivers and health care insurers to compare options when shopping for long-term care facilities.

Alzheimer's Disease Centers Program

The NIA funds 28 Alzheimer's Disease Centers (ADC's) at major medical institutions across the Nation. The centers conduct a wide range of research, including studies on the causes of AD and investigations aimed at diagnosing, treating, and managing the symptoms of the disease. The ADC Program promotes research, training and education; technology sharing; and multi-center and cooperative studies of diagnosis and treatment. Each ADC has administrative, clinical, neuropathology, and education and information-sharing cores, or sections. Some ADC's include additional cores, such as neuroimaging and data analysis.



Much of the success of AD research in this country during the last 10 years can be attributed to resources provided at the Alzheimer's Disease Centers.

ADVANCES IN TREATING AND PREVENTING ALZHEIMER'S DISEASE

Fifteen comprehensive ADC's have fully-funded basic, clinical, and behavioral research projects. Areas of study range from the basic mechanisms of AD to managing the symptoms and helping families cope with the effects of the disease. The other 13 ADC's are Alzheimer's Disease Core Centers, which provide resources to AD researchers.

A program was initiated in 1990 to add satellite clinics linked to the ADC's. Currently, 27 satellite clinics at 21 ADC's offer diagnostic and treatment services and collect research data in underserved, rural, and minority communities. These programs allow members of culturally and ethnically diverse communities to take part in research and clinical drug trials associated with parent ADC's.

Much of the success of AD research in this country during the last 10 years can be attributed to resources provided at the ADC's, including the recent discovery of the importance of chromosome 14 in FAD and the identification of inherited risk factors related to ApoE. The ADC's enhance AD research by providing a network for sharing new ideas as well as research results.

Other initiatives funded by the NIA depend on the ADC's, including regular research grants, the Consortium to Establish a Registry for Alzheimer's Disease, and the ADCSU. The ADC's provide resources for these efforts, such as patient data, brain and other tissue samples, and molecular probes.

RESEARCH CONDUCTED BY OTHER NIH INSTITUTES

National Institute of Diabetes and Digestive and Kidney Diseases

National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) research that relates to AD generally falls within two areas. The first focuses on mechanisms involved in abnormal metabolic processes. The second concerns the molecular and biochemical mechanisms of cells, including the roles of neurotransmitters and ion channels.

This year, NIDDK grantees reported progress in understanding the metabolic processes leading to the formation of abnormal amyloid protein, a major component of plaques in the brain. Although the ultimate cause of neuronal cell death remains undetermined, some evidence suggests that the buildup of abnormal amyloid protein may be involved in this process.

One goal of NIDDK-supported research is to understand the biochemical mechanisms underlying amyloid diseases. Researchers are learning how APP, a normally soluble protein, is transformed into the insoluble fibers that build up in AD plaques. This work focuses on a form of abnormal amyloid protein that has been implicated in amyloid polyneuropathy, a neurologic disease. This form of abnormal amyloid protein is similar but not identical to the form found in AD. These researchers identified a gene mutation that alters an intermediate step in the formation of amyloid and appears to be related to abnormal amyloid protein production. The findings suggest that certain gene mutations may have metabolic effects that determine the development of amyloid disease.

RESEARCH CONDUCTED BY OTHER NIH INSTITUTES

National Institute of Neurological Disorders and Stroke

The National Institute of Neurological Disorders and Stroke (NINDS) is the principal source of support for neurological research in the United States and a major participant in the study of AD. Basic studies are aimed at determining the underlying causes of AD with the ultimate goal of prevention. Clinical research seeks to improve the diagnosis and treatment of patients.

Scientists at the NINDS and NIA have discovered that adding beta-amyloid to normal skin cells causes them to undergo the same type of failure at the molecular level previously shown in skin cells of patients with AD. By placing a solution with low levels of beta-amyloid in culture with normal human skin cells, the scientists produced changes in potassium channel function similar to those seen in skin cells from AD patients. Beta-amyloid is the main component of plaques found in brain tissue in AD. This finding suggests that beta-amyloid may cause the abnormal process that leads to memory loss even before it congeals into plaques. This research may lead to alternative explanations of the causes of memory loss, one of the earliest and most common symptoms of the disease.

RESEARCH CONDUCTED BY OTHER NIH INSTITUTES

Last year, researchers in the same laboratory showed that skin cells from people with AD have defects that interfere with the cell's ability to regulate its concentrations of potassium and calcium ions. The flow of potassium and consequent uptake of calcium are especially critical in brain cells responsible for memory formation and information storage.

Recently, after treating one group of the skin cells with soluble beta-amyloid for 48 hours, scientists found that a specific potassium channel was absent in all but one of the cells. However, a functional potassium channel was present in 94 percent of untreated cells. Results of further testing suggest that beta-amyloid selectively targets this specific potassium channel, which had been absent in skin cells of AD patients.

These researchers now are working to see if similar potassium channel dysfunction occurs in central nervous system neurons. The scientists have discovered similar defects in nerve cells of the olfactory system (related to the sense of smell), suggesting that such defects may be present in brain cells.

RESEARCH CONDUCTED BY OTHER NIH INSTITUTES

National Institute of Arthritis and Musculoskeletal and Skin Diseases

Researchers at the National Institute of Arthritis and Musculoskeletal and Skin Diseases have made strides in finding a treatment for amyloidosis (a buildup of amyloid protein in various body tissues). This research may lead to a possible treatment for AD, because a major feature of AD is brain deposits of amyloid or amyloid-like material.

Some forms of amyloidosis are inherited. One of these forms, familial amyloid polyneuropathy (FAP), is caused by a mutation of the transthyretin (TTR) protein. Scientists have developed a method for separating normal and mutant TTR in bodily fluids, allowing rapid screening and diagnosis. This method also allows the ratio of normal to mutant TTR to be measured over time.

These researchers also have reported on liver transplants in patients with FAP. Almost all normal and abnormal TTR is produced in the liver. Patients undergoing liver transplants for advanced disease showed important improvements in their conditions. The amount of mutant TTR present after the transplant was reduced markedly. After surgery, patients had only normal TTR. This is the first successful therapy in patients with FAP.

National Institute on Deafness and Other Communication Disorders

The National Institute on Deafness and Other Communication Disorders (NIDCD) studies the normal and disordered processes of balance, smell, taste, voice, speech, hearing, and language. The NIDCD's chemosensory (smell and taste) research program includes studies of the olfactory receptor cell (a nerve cell in the part of the nose

RESEARCH CONDUCTED BY OTHER NIH INSTITUTES

that senses smell). Normally, these nerve cells are replaced continually in the body. An important aspect of this research is the potential for developing new strategies to treat nerve cell loss caused by aging, injury, and diseases, such as AD.

Scientists supported by the NIDCD recently examined the development of human olfactory neurons transplanted into the brains of animals. They studied the interaction of these transplanted neurons with other brain cells. The transplanted neurons not only survived, but developed and grew nerve fibers that entered and mingled with the animal's other nerve cells. The fact that donor olfactory neurons developed and integrated with other nerve cells means that the possibility exists of forming new neuronal connections.

The capacity of transplanted olfactory neurons to produce new nerve cells is of wide interest not only with respect to chemosensory function, but also as a model for studying neuron replacement. Further research on transplanted neurons may show that biological repair of nerve damage from neurodegenerative diseases, including AD, is possible.

National Institute of Mental Health

National Institute of Mental Health (NIMH) research on AD spans from the genetics and molecular biology of the disease to the psychosocial stresses faced by family members.

The NIMH Diagnostic Centers for Psychiatric Linkage Studies of Alzheimer's Disease identify siblings with and without AD for ongoing studies. The centers' goal is to establish a national resource of cell lines and clinical data from people with AD and their key relatives.

RESEARCH CONDUCTED BY OTHER NIH INSTITUTES

Advances in the molecular genetic study of AD may show how the disorder develops and offer ways to identify those at risk for the purposes of early intervention. Neurofibrillary tangles found in the AD brain largely consist of abnormal forms of the cellular protein *tau*. In the normal brain, *tau* binds to microtubules that provide structural support for cells, including neurons. In AD, *tau* takes the form of twisted fibers and does not bind to microtubules.

Using techniques from molecular genetics, NIMH researchers have identified tissue at risk for AD and other neurodegenerative processes. They also have developed a new probe, an antibody that identifies and interacts exclusively with neurons that are vulnerable to the disease. Antibodies are immune system molecules. Antigens stimulate the production of antibodies. Each antibody has a unique amino acid sequence that allows it to interact with only a certain antigen. The above antibody probe stains for a different antigen than expected. This finding suggests that a host of unknown pathologic indicators or gene products may occur in AD.

RESEARCH CONDUCTED
BY OTHER NIH INSTITUTES

In test tube studies, NIMH scientists have been able to grow neuroblasts (immature nerve cells), which were taken from inside the noses of AD patients and healthy people. They have found that AD neuroblasts have increased levels of APP fragments. These fragments are thought to include the toxic protein beta-amyloid. The amount of fragments decreases when theophylline is added to the cells, suggesting toxicity and a potential therapeutic intervention.

Recent advances in basic neuroscience research link brain structures and functions involved in AD and help explain some AD symptoms. Using animal models, NIMH-supported researchers have found a connection between two areas of the brain, one of which allows people to forget an emotion-linked memory that no longer is useful. When this part of the brain is damaged, it may fail to erase an emotional memory or prevent an emotional response. This research may bear on AD patients' inappropriate emotional responses or inability to remember emotionally significant information.

NIMH researchers strive to reduce problematic symptoms of AD and help families care for these patients. They are studying the relationship between disturbed sleep, altered sleep-wake cycles, episodes

RESEARCH CONDUCTED
BY OTHER NIH INSTITUTES

of stopped breathing, daytime sleepiness, and sundowning (or nighttime confusion). By doing so, NIMH-funded researchers hope to decrease sleep problems and confusion and reduce some disability in AD patients. Preliminary studies of patients with dementia and normal breathing during sleep show they have less confusion in the morning or the same amount of confusion as during the previous night. This finding suggests that increased confusion related to a decrease in the amount of oxygen breathed in during sleep may represent an early phase of sundowning. Studies also are being done of the clinical efficacy of several medications commonly used for sundowning.

An NIMH-supported program for caregiving spouses of AD patients delayed nursing home placements up to 6 months. This program offered individual and family counseling and a caregiver support group. Compared to other caregivers not in the program, the supported spouses showed less decline in their own mental and physical health, and derived more satisfaction from their social support networks. Results suggest that psychosocial interventions may relieve some burdens of long-term caregiving for chronically impaired older adults. This relief may translate into major cost reductions for health care delivery systems. These findings are important, given the high cost of nursing home care and the increasing number of people with AD.

RESEARCH CONDUCTED BY OTHER NIH INSTITUTES

NIMH-funded research indicates that caregiving stress negatively affects the caregiver's mental health (increased depression), immune system function, and physical health. These studies show that AD caregivers perform lower on measures of their bodies' ability to fight diseases and have more infectious disease episodes than do non-caregivers. Older, caregiving spouses' immune functions fail to return to the level found in controls over a sustained period. Caregivers also show a lower antibody buildup in response to influenza vaccination.



An NIMH-supported program for caregiving spouses of AD patients delayed nursing home placements up to 6 months. This program offered individual and family counseling and a caregiver support group.

Male caregivers may be at risk for the cardiovascular effects of caregiving stresses. Higher levels of triglycerides ("bad" cholesterol) and lower levels of high-density lipoproteins ("good" cholesterol) have been found among male caregivers. Male caregivers also have higher levels of: anger, coronary-prone behavior, and use of avoidance when coping. These results provide the foundation for more targeted interventions with caregivers who can be identified as more or less at risk for mental health and physical health problems.

RESEARCH CONDUCTED BY OTHER NIH INSTITUTES

Although most older Americans lead healthy lives unaffected by significant mental disorder, up to 12 percent of people age 65 and older experience an anxiety disorder, depression, or some form of dementia. Mental disorders in late life are not an outcome of normal aging. Instead, they are illnesses that result in significant disability, dependency, and early death. Sleep problems can lead to inappropriate use of sleeping pills, fatigue, and disorientation, which in turn reduce quality of life and increase the chances of illness. Of the 5 percent of older Americans in nursing homes, up to one-fifth suffer from some form of unnecessary depression, which increases the risk of mortality.

Mental disorders in older people often occur along with physical illness and pain symptoms. Older people are less likely to seek mental health services, and many seek assistance from primary care physicians when faced with mental illness. Unfortunately, mental disorders in older people typically go undetected, and many do not receive available treatments. This is particularly tragic for depressed older people who commit suicide. More than 70 percent of older men (the highest risk group for suicide in this country) visit their primary care physicians within 1 month before committing suicide.

RESEARCH CONDUCTED BY OTHER NIH INSTITUTES

Safe and effective treatments are available for depression, anxiety, and sleep disorders. Efforts to refine treatments include studies of how people metabolize psychotropic medications (drugs that act on the mind) with and without other medications for physical disorders. Research on psychosocial treatments alone and in combination with medications over long periods are providing important data for recommended treatment practices. Like other diseases, it appears that many mental disorders require long-term treatments.

National Center for Research Resources

Through its national network of clinical, animal, and other research resource centers, the National Center for Research Resources (NCRR) supports studies to advance understanding and treatment of AD and other disorders affecting older Americans.

In addition to research at Duke University on ApoE (see pages 9-10), the NCRR supports several potential therapies for AD at Regional Primate Research Centers (RPRC's). Researchers at the University of Washington RPRC have used a compound (leupeptin) that accelerates brain aging in rats to stimulate an effect similar to AD in aged monkeys.

RESEARCH CONDUCTED BY OTHER NIH INSTITUTES

At the California RPRC, scientists found that age-related neuron weakening in part of the brain can be prevented by adding nerve growth factor (NGF) in primates. An NGF is a protein that fosters development of nerve cells and may protect certain nerve cells from damage. It supports cells that produce the vital neurotransmitter, acetylcholine. Other neurotrophic factors (components that help maintain body tissues and are regulated by nervous functions) also may be useful in therapy for this degeneration. Using gene therapy techniques, researchers have found that NGF-producing fibroblasts (cells that are part of the tissue that binds together and supports the various body structures) survive up to 6 months in the adult primate brain.

At the Wisconsin RPRC, scientists are mapping the distribution of neurotrophins and their receptors. This work will help identify growth factors that may allow rescue of neurons in brain regions affected by AD.

National Eye Institute

The National Eye Institute continues to support a study of human binocular vision and motion perception. Binocular vision is the merging of images from both eyes into a single image perceived by the visual cortex of the brain. Motion perception is the ability to perceive clearly the direction and speed of a moving object. This research focuses on interactions among the neurological mechanisms underlying these aspects of vision and stereopsis. Stereopsis is the ability to combine the images

RESEARCH CONDUCTED BY OTHER NIH INSTITUTES

of two pictures of an object seen from slightly different viewpoints. It refers to how people see something as both a solid and three-dimensional object. These study areas may provide important clues about the perceptual consequences of neurologic dysfunctions in AD. Specific areas under study are: the coexistence of stereopsis and binocular competition; the regions in the brain associated with binocular suppression (relative to the analysis of motion information) and visual attention; interactions between stereopsis and depth perception in specifying structure from motion; and motion perception and stereopsis in AD patients.

National Institute of Allergy and Infectious Diseases

Studies conducted by the National Institute of Allergy and Infectious Diseases (NIAID) with the greatest relevance to aging and AD involve research to develop a drug to prevent scrapie. Scrapie is an infectious, neurodegenerative disease of sheep and goats. Scrapie is similar to AD in that accumulations of abnormal protein form amyloid plaques in the brain. One advantage of scrapie research is that, unlike AD research, animal and cell culture models already exist in which to study amyloid formation and therapeutic strategies. Current NIAID research on scrapie offers potential for understanding the clinical development of AD.

The agent that causes scrapie is an unusual infectious particle that contains no nucleic acid and consists of a single protein, called PrP-res.

RESEARCH CONDUCTED BY OTHER NIH INSTITUTES

NIAID scientists found that when a normal protein typically found in the brain (PrP-sen) interacts with an altered form of itself, the altered form is converted to PrP-res. When PrP-res builds up in the brain, amyloid plaques form. Although the major proteins forming plaques differ in scrapie and AD, an understanding of how amyloid is formed in scrapie may provide insights about plaque formation in the AD brain.

NIAID intramural scientists have found that Congo red, a chemical dye, can delay the onset of scrapie in mice by preventing the buildup of PrP-res in the brain infected with scrapie. The fact that Congo red shows some efficacy in preventing the development of scrapie in laboratory animals suggests that a similar substance might be useful in preventing the development of AD in humans.

NIAID scientists also are conducting test tube studies related to aging. Using a new technique, NIAID researchers have isolated almost all classes of stem cells (the earliest developmental form of blood cells) from mouse bone marrow. This isolation process does not appear to alter the cells' normal behavior, suggesting that stem cells are reliable for studying normal blood cell development. Isolated stem cells now can be used to evaluate the effects of the aging process on blood cell development.

OUTLOOK

Scientists have learned a great deal about AD in the past year. Projects in 1995 will seek to identify the gene on chromosome 14 responsible for one form of early-onset AD and to understand better how ApoE works as a risk factor for AD. More specifically, researchers are interested in learning how ApoE relates to plaques and tangles. Scientists also will look for ways to enhance the use of imaging techniques, especially MRI, as early diagnostic or predictive tools for AD. Improved MRI technology is expected to allow researchers to identify initial changes in the hippocampus in AD. PET scans eventually may detect changes in brain metabolism that precede AD onset by as much as 20 years. PET scans also may monitor possible drug therapies that could prevent the severe nerve damage and memory loss that occur in AD patients. Clinical studies of estrogen and anti-inflammatory agents will build on evidence gained from previous epidemiologic studies. Another important area of research in the next few years will focus on behavioral interventions for patients and training programs for caregivers. Taken together, these avenues of research will help scientists to understand the causes of AD, to diagnose the disease earlier, and to improve treatment and caregiving strategies.



Older Americans Month
—May—

National Grandparents
Day — 1st Sunday in
Sept. after Labor
Day (Sept 8 1996)

National Alzheimer's
Disease Month — NOV.

Alzhe Disea

Beelby

4 page

AD FACT SHEET

2

AD is named after Dr. Alois Alzheimer, a German doctor. In 1906, Dr. Alzheimer noticed changes in the brain tissue of a woman who had died of an unusual mental illness. He found abnormal clumps (now called senile or neuritic plaques) and tangled bundles of fibers (now called neurofibrillary tangles). Today, these plaques and tangles in the brain are considered hallmarks of AD.

Scientists also have found other changes in the brains of people with AD. There is a loss of nerve cells in areas of the brain that are vital to memory and other mental abilities. There also are lower levels of chemicals in the brain that carry complex messages back and forth between billions of nerve cells. AD may disrupt normal thinking and memory by blocking these messages between nerve cells.

Symptoms

AD begins slowly. At first, the only symptom may be mild forgetfulness. People with AD may have trouble remembering recent events, activities,

3

or the names of familiar people or things. Simple math problems may become hard for these people to solve. Such difficulties may be a bother, but usually they are not serious enough to cause alarm.

However, as the disease goes on, symptoms are more easily noticed and become serious enough to cause people with AD or their family members to seek medical help. For example, people with AD may forget how to do simple tasks, like brushing their teeth or combing their hair. They can no longer think clearly; and they begin to have problems speaking, understanding, reading, or writing. Later on, people with AD may become anxious or aggressive, or wander away from home. Eventually, patients may need total care.

Diagnosis

Doctors at specialized centers can diagnose probable AD correctly 80 to 90 percent of the time. They can find out whether there are plaques and tangles in the brain only by looking at a piece of brain tissue under a micro-

AD is the most common cause of dementia in older people.

A dementia is a medical condition that disrupts the way the brain works. AD affects the parts of the brain that control thought, memory, and language. Every day, scientists learn more about AD, but right now the cause of the disease still is unknown, and there is no cure. An estimated 4 million people in the United States suffer from AD.

The disease usually begins after age 65, and risk of AD goes up with age. While younger people also may have AD, it is much less common. About 3 percent of men and women ages 65 to 74 have AD, and nearly half of those age 85 and older may have the disease. It is important to note, however, that AD is **not** a normal part of aging.



Alzheimer's Disease Education &
Referral Center
A Service of the National Institute on Aging

Fact Sheet

Fact Sheet

Fact Sheet

scope. It can be painful and risky to remove brain tissue while a person is alive. Doctors cannot look at the tissue until they do an autopsy, which is an examination of the body done after a person dies.

Doctors may say that a person has "probable" AD. They will make this diagnosis by finding out more about the person's symptoms. The following is some of the information the doctor may need to make a diagnosis:

- **A complete medical history—** The doctor may ask about the person's general health and past medical problems. He or she will want to know about any problems the person has carrying out daily activities. The doctor may want to speak with the person's family or friends to get more information.
- **Basic medical tests—** Tests of blood and urine may be done to help the doctor eliminate other possible diseases. In some cases, testing a small amount of spinal fluid also may help. In addition, scientists are busy trying to develop a test to diagnose AD that will be easy and accurate.

- **Neuropsychological tests—** These are tests of memory, problem solving, attention, counting, and language. They will help the doctor pinpoint specific problems the person has.
- **Brain scans—** The doctor may want to do a special test, called a brain scan, to take a picture of the brain. There are several types of brain scans, including a computerized tomography (CT) scan, a magnetic resonance imaging (MRI) scan, or a positron emission tomography (PET) scan. By looking at a picture of the brain, the doctor will be able to tell if anything does not look normal.

Information from the medical history and any test results help the doctor rule out other possible causes of the person's symptoms. For example, thyroid gland problems, drug reactions, depression, brain tumors, and blood vessel disease in the brain can cause AD-like symptoms. Some of these other conditions can be treated.

Treatment

AD is a slow disease, starting with mild memory problems and ending with severe mental damage. The course the disease takes and how fast changes occur vary from person to person. Some people only have the disease for 5 years, while others may have it for as many as 20 years.

No treatment can stop AD. However, for some people in the early and middle stages of the disease, the drug tacrine (also known as THA or Cognex) may alleviate some cognitive symptoms. Also, some medicines may help control behavioral symptoms of AD such as sleeplessness, agitation, wandering, anxiety, and depression. Treating these symptoms often makes patients more comfortable and makes their care easier for caregivers.

Scientists are testing new drugs for AD at many large teaching hospitals and universities. Some of these drugs have shown promise in easing symptoms in some patients. People with AD who want to help scientists test these experimental drugs may be able to take part in clinical trials. To find

out more about these studies, contact the Alzheimer's Disease Education and Referral (ADEAR) Center at the telephone number listed at the end of this fact sheet.

People with AD should go to their doctor regularly. The doctor will check to see how the disease is progressing and treat any other illnesses that occur. The doctor and other health professionals also can offer help and support to patients and their families.

Most often, spouses or other family members provide the day-to-day care for people with AD. As the disease gets worse, people often need more and more care. This can be hard for caregivers and can affect their physical and mental health, family life, jobs, and finances.

The Alzheimer's Association has chapters nationwide that provide educational programs and support groups for caregivers and family members of people with AD. For more information, contact the Alzheimer's Association listed at the end of this fact sheet.

Research

Scientists at research centers across the country are trying to learn what causes AD and how to prevent it. They also are studying how memory loss happens. They are looking for better ways to diagnose and treat AD, to improve the abilities of people with the disease, and to support caregivers.

The major risk factors for AD are age and family history. Other possible risk factors include a serious head injury and lower levels of education. Scientists also are studying additional factors to see if they may cause the disease. Some of these factors include:

- **Genetic (inherited) factors**—Scientists believe that genetic factors may be involved in more than half of the cases of AD. For example, a protein called apolipoprotein E (ApoE) may be important. Everyone has ApoE, which helps carry cholesterol in the blood. However, the function of ApoE in the brain is less understood. The ApoE gene has three forms. One form seems to protect a person from AD, and an-

other form seems to make a person more likely to develop the disease. Scientists still need to learn a lot more about ApoE and its role in AD.

- **Environmental factors**—Scientists have found aluminum, zinc, and other metals in the brain tissue of people with AD. They are studying these metals to see if they cause AD or if they build up in the brain as a result of the disease.
- **Viruses**—Some scientists think that a virus may cause AD. They are studying viruses that might cause the changes seen in the brain tissue of people with AD.

AD probably is not caused by any one factor. It is more likely to be several factors that act differently in each person. For example, genetic factors alone may not be enough to cause the disease. Other risk factors may combine with a person's genetic makeup to increase his or her chance of developing the disease.

Scientists also are trying to develop a test that can detect or predict AD. If the onset of the disease could be

delayed for even a short time, the number of people with the disease would drop. Delaying AD also would make the quality of life better for older people and lead to savings in health care costs.

Other research is aimed at helping both patients and caregivers cope with the patients' loss of abilities and the stress this causes. For example, researchers are studying ways to manage problem behaviors in patients, such as wandering and agitation. Still other scientists are evaluating services and programs for patients and caregivers, including respite care. Respite care covers a variety of situations in which someone else cares for the patient for a period of time, giving family caregivers temporary relief.

The National Institute on Aging, the Federal Government's lead agency for AD research, funds Alzheimer's Disease Centers located throughout the United States. The centers carry out a wide range of research, including studies on the causes, diagnosis, treatment, and management of AD. To obtain a

list of the centers, contact the ADEAR Center listed below.

For More Information

To learn about support groups, services, research centers, and publications about AD, contact the following groups:

Alzheimer's Association
919 N Michigan Avenue, Suite 1000
Chicago, IL 60611-1676
800-272-3900

This non-profit group supports families and caregivers of AD patients. Chapters nationwide provide referrals to local resources and services, and sponsor support groups and educational programs.

Alzheimer's Disease Education and Referral (ADEAR) Center
PO Box 8250
Silver Spring, MD 20907-8250
800-438-4380

This service of the National Institute on Aging is funded by the Federal Government. It offers information and publications on diagnosis, treat-

ment, patient care, caregiver needs, long-term care, education and training, and research related to AD. Staff respond to telephone and written requests and make referrals to national- and State-level resources.

Eldercare Locator

1112 16th Street NW, Suite 100
Washington, DC 20036
800-677-1116

This service of the National Association of Area Agencies on Aging provides information about and referrals to respite care and other home and community services offered by State and Area Agencies on Aging.



U.S. DEPARTMENT OF HEALTH
AND HUMAN SERVICES
Public Health Service
National Institutes of Health
National Institute on Aging

NIH Publication No. 95-3431

August 1995

595TH STORY of Level 1 printed in FULL format.

Copyright 1994 The New York Times Company
The New York Times

November 6, 1994, Sunday, Late Edition - Final

SECTION: Section 1; Page 1; Column 1; National Desk

LENGTH: 1203 words

HEADLINE: In Poignant Public Letter, Reagan Reveals That He Has Alzheimer's

BYLINE: By MICHAEL R. GORDON, Special to The New York Times

DATELINE: WASHINGTON, Nov. 5

BODY:

Former President Ronald Reagan said today that he had entered the early stages of Alzheimer's disease, an incurable brain ailment that steadily destroys memory and eventually leads to death.

In a handwritten letter to the American people, the 83-year-old Mr. Reagan said he was in good health now, and while he maintained a positive tone, he did strike a fatalistic note.

"I now begin the journey that will lead me into the sunset of my life," Mr. Reagan wrote. "I know that for America there will always be a bright dawn ahead." [Text of the letter, page 47.]

Mr. Reagan's letter, issued by his office in Los Angeles, was accompanied by a statement from his doctors, who explained that the disease was diagnosed through repeated observations and testing for a year.

"Over the past 12 months we began to notice from President Reagan's test results symptoms indicating the possibility of early-stage Alzheimer's disease," the doctors wrote. "Additional testing and an extensive observation over the past few weeks have led us to conclude that President Reagan is entering the early stages of this disease."

The doctors said that Mr. Reagan's current health was good, but "it is expected that as the years go on it will begin to deteriorate."

Alzheimer's disease is an incurable neurological disorder, which affects communication between brain cells and, ultimately, causes the cells to die.

The disease leads to memory loss, which can produce disorientation, difficulty in speaking and personality disorders. It afflicts about four million people in the United States. Most victims are older than 65.

At a Democratic rally in Alameda, Calif., this afternoon, President Clinton asked the crowd to put its partisanship aside and wish Mr. Reagan well, and then he passed on the news that Mr. Reagan was suffering from Alzheimer's disease.

The New York Times, November 6, 1994

Mr. Clinton recalled a visit with Mr. Reagan shortly after his own election and said there had come a point when the former President stopped and said he had forgotten what he was going to say.

"When he said that, it touched my heart in a particular way," Mr. Clinton said.

While he was the President, Mr. Reagan had a relaxed leadership style and was known for occasionally becoming disengaged and bored during White House meetings. His associates said that in recent months he had changed markedly and that he was failing to recognize people he had known. Some longtime friends of Mr. Reagan said tonight that the former President's memory had begun to slip noticeably for two years.

"You could tell that he had it as early as, say, two years ago," said an associate who spent considerable time with the former President in recent years. "He was having a definite memory problem, and he'd say time and again, 'I just can't remember.'"

"He talked at times about his memory problems," said the associate, who spoke only on the condition that he not be publicly identified. "He even mentioned that his mother had died of Alzheimer's, and he wondered whether he might have inherited it. But then he'd go on in his usual breezy manner and that would be the end of the discussion."

The oldest man ever to serve as President, Mr. Reagan said when he was elected in 1980 at age 69 that he would have the White House physician test him periodically and that he would resign if serious evidence of senility or mental deterioration were detected.

"If I were President and had any feeling at all that my capabilities had been reduced before a second term came," he said at the time, "I would walk away. By the same token, I would step down also."

He was elected by overwhelming margins in 1980 and 1984, touting his program to cut taxes, strengthen the military and reduce the deficit.

On foreign policy, Mr. Reagan was more pragmatic than his cold war talk suggested. But his supply-side economics led to soaring deficits.

During his final year in office, he was politically hobbled by the Iran-contra scandal. But while the Iran-contra affair claimed many victims, Mr. Reagan's popularity was relatively unscathed.

During office, he survived an assassination attempt in which he was shot in the chest. He has also been operated on to remove cancerous polyps from his colon and has had prostate surgery.

After retiring, Mr. Reagan remained physically vigorous. In 1989, he surgeons removed fluid from his brain, apparently the result of his having been thrown from a horse.

One associate speculated that Mr. Reagan's family decided to issue a public announcement today because his behavior was becoming too difficult to ignore. Even so, many old friends were shocked.

The New York Times, November 6, 1994

"It catches me totally by surprise," said Fred F. Fielding, who was Counsel to the President from 1981 to 1986.

Sheila Tate, who served as Mrs. Reagan's press secretary, fought back tears tonight. "The letter was quite emotional," she said. "But it was so like Ronald Reagan to do something like this -- so gracefully."

Ms. Tate said that she had spoken at length with the former First Lady earlier this week but that Mrs. Reagan had provided no clue that she was under any special strain. "She was in good humor," Ms. Tate said. "We talked about everything, from politics to politics."

In his two-page letter, Mr. Reagan said he had decided to make his condition known to raise public awareness of Alzheimer's disease after discussion with his wife.

"I have recently been told that I am one of the millions of Americans who will be afflicted with Alzheimer's disease," Mr. Reagan wrote in his hand-written letter, which was faxed to news organizations. "Upon learning this news, Nancy and I had to decide whether as private citizens we would keep this as a private matter or whether we would make this news known in a public way.

"In opening our hearts, we hope this might promote greater awareness of this condition. Perhaps it will encourage a clearer understanding of the individuals and families who are affected by it."

Mr. Reagan said he felt "just fine" and planned to spend his time with his wife and family and to enjoy the outdoors in California.

He thanked the American people for electing him.

His letter was written in a steady hand, his writing marred only when he speculated about his death. In that passage, Mr. Reagan crossed out two words and then continued his phrase.

"When the Lord calls me home, whenever that may be, I will leave with the greatest love for this country of ours and eternal optimism for the future," he wrote. "I now begin the journey that will lead me into the sunset of my life. I know that for American there will always be a bright dawn ahead."

At the Democratic rally, Mr. Clinton, recalled Mr. Reagan's sense of optimism.

"We disagreed on a lot of things over the years," the President said of his predecessor. "But he always fought with a sense of optimism and spirit."

Mr. Clinton said he was particularly grateful for Mr. Reagan's support in the last year for the North American Free Trade Agreement, the ban on assault weapons and for criticizing Oliver L. North in the Virginia Senate campaign.

"I want every one of you in this room to give Ronald Reagan a hand and wish him well and goodness," Mr. Clinton said.

LANGUAGE: ENGLISH

592ND STORY of Level 1 printed in FULL format.

Copyright 1994 The Times Mirror Company
Los Angeles Times

November 6, 1994, Sunday, Home Edition

SECTION: Part A; Page 1; Column 2; Metro Desk

LENGTH: 1893 words

HEADLINE: REAGAN SAYS HE IS IN EARLY STAGES OF ALZHEIMER'S

BYLINE: By BETTINA BOXALL and DEBORAH SCHOCH, TIMES STAFF WRITERS

BODY:

In a poignant, hand-penned letter to the American public, former President Ronald Reagan disclosed Saturday that he is suffering from the early stages of Alzheimer's disease.

"I now begin the journey that will lead me into the sunset of my life," Reagan, 83, wrote to "my fellow Americans."

Saying that at the moment he feels "just fine," Reagan explained that he was going public with his diagnosis to promote broader awareness of the disease -- a progressive, irreversible neurological disorder that kills more adults in the United States than any ailment except heart disease, cancer or strokes.

In an accompanying statement released by his Los Angeles office, Reagan's five personal physicians said the condition was discovered during routine medical testing.

"Over the past 12 months we began to notice from President Reagan's test results symptoms indicating the possibility of early stage Alzheimer's disease," the doctors wrote. "Additional testing and an extensive observation over the past few weeks have led us to conclude that President Reagan is entering the early stages of this disease."

In the two-page letter, Reagan, who lives in Bel-Air, maintained his characteristic cheerfulness.

"I intend to live the remainder of the years God gives me on this earth doing the things I have always done," he said. "I will continue to share life's journey with my beloved Nancy and my family. I plan to enjoy the great outdoors and stay in touch with my friends and supporters."

Friends reacted with sober acceptance, some acknowledging that Reagan had seemed to be losing mental acuity.

Catherine Busch, spokeswoman for Reagan, said Saturday afternoon that the former President was with his wife at an undisclosed California location outside Los Angeles. Busch declined further comment, saying, "The letter speaks for itself."

Los Angeles Times, November 6, 1994

The nation's oldest President, Reagan was treated for several medical problems during his two terms in the White House. He underwent surgery for a prostate gland condition and a colon cancer lesion during his second term and was wounded in an assassination attempt shortly after he took office in 1981.

A perpetual optimist, Reagan told a reporter after his successful colon surgery: "I didn't have cancer. I had something inside of me that had cancer in it and it was removed."

In his letter -- so informal that it included a scratched-out phrase -- Reagan wrote: "In the past Nancy suffered from breast cancer and I had my cancer surgeries. "We found through our open disclosures we were able to raise public awareness.

"So now, we feel it is important to share it with you," Reagan continued. "In opening our hearts, we hope this might promote greater awareness of this condition. Perhaps it will encourage a clearer understanding of the individuals and families who are affected by it."

He added: "Unfortunately, as Alzheimer's disease progresses, the family often bears a heavy burden. I only wish there was some way I could spare Nancy from this painful experience. When the time comes I am confident that with your help she will face it with faith and courage."

Around the country, Reagan's friends, political allies and foes expressed sadness at the news, as well as admiration for the manner in which the former California governor and Hollywood actor was handling it.

"Typical Gipper," former Reagan speech writer Ken Khachigian said affectionately when Reagan's letter was read to him.

Khachigian said he had not seen Reagan for a couple of years but had heard reports "that he was somewhat less engaged. A lot of us who had been close to him thought that was just the normal aging process.

"But obviously this gives a more understandable medical explanation of why he was slowing down a bit," added Khachigian, an attorney and political consultant. "(It was) courageous of him as usual to come out with something like this. And I'm sure that over the next few years we'll see that he'll continue to have a sunny disposition, that he'll have his sunny, optimistic view of life."

In Oakland, President Clinton spoke of Reagan in his remarks to several thousand Democratic activists Saturday afternoon.

"I'm going to ask you to do something we normally wouldn't do at a Democratic rally," Clinton said, asking the boisterous group to remain silent while he made an announcement. A low murmur of dismay could be heard rippling through the crowd as he told them of Reagan's condition.

"It touched my heart," Clinton said of the news.

He went on to recount a story of having met with Reagan not long after Clinton's election as President. The two conversed about the job, and at one point, Clinton said, Reagan looked at him and said, "You know, I forgot what I

Los Angeles Times, November 6, 1994

was talking about, and it really makes me mad."

He and Reagan "disagreed on a lot of things," Clinton said, but he praised the former President for his decency. "He always fought with a sense of optimism and spirit," Clinton said.

He added that Reagan had been "willing to put partisanship aside" and help him on issues such as the North American Free Trade Agreement and the Brady Bill limiting handgun sales, which was named after Reagan's former press secretary, James Brady. "I want everyone of you in this room now to give Ronald Reagan a hand and wish him Godspeed," Clinton said. The audience applauded.

In Houston, former President George Bush released a statement saluting Reagan "for his courage and (for) sharing this private matter with the American people. Barbara and I are thinking of our good friends, Ron and Nancy, and we wish them well." After the announcement was made, former Reagan staff members began phoning one another.

"We were all caught off guard here," said Sheila Tate, who was Nancy Reagan's press secretary. "We're calling each other and feeling sad for him, and for her."

Tate said a friend saw the news on CNN and contacted her at her McLean, Va., home. Tate immediately turned on her television.

"I saw the handwritten letter, which I thought was incredibly moving and quintessentially Ronald Reagan," said Tate. In dealing with the disease, she said, Reagan thought about how he could help other people. "It's typical of how he's approached his whole life."

During his presidency, Reagan's age and health periodically became issues, particularly when he seemed unsure or forgetful. He would shrug off the concerns with jokes and made a point of being photographed while riding horseback on vacation.

He continued to make public statements and appearances after leaving office six years ago. Last spring he declared himself "pretty steamed" over Iran-Contra figure Oliver L. North's comments that Reagan had approved North's role in the illegal arms deal. But in recent years he had assumed a lower profile, attending fewer events and declining interviews. He appeared in failing health at last spring's funeral of former President Richard Nixon.

Reagan's physicians -- including Dr. Leslie Weiner of USC and Dr. James R. Blake of St. John's Hospital in Santa Monica -- said that although Reagan's health is otherwise good, "it is expected that as the years go on it will begin to deteriorate."

"Unfortunately, at this time, there is no cure for Alzheimer's disease and no effective treatment exists that arrests its progression," the doctors noted, adding that they would have no further comment about Reagan's condition.

Reagan's mother, Nelle, who died at age 77, also apparently suffered from Alzheimer's.

Los Angeles Times, November 6, 1994

Dr. Jeffrey L. Cummings, director of the UCLA Alzheimer's Disease Center, said that judging from the coherence of Reagan's letter, he appears to be in the early stages of the disease.

Cummings said he expected that the announcement would focus attention on Alzheimer's disease as news of Earvin (Magic) Johnson's illness in 1991 did on AIDS.

About 4 million Americans suffer from Alzheimer's disease, which is characterized by a progressive loss of mental function, including memory and language. About 100,000 people die of the disease each year.

As many as 50% of those over 85 are thought to have Alzheimer's, although it can also strike people in their 40s or 50s.

The average time from diagnosis to death is generally seven to 10 years, although some may die sooner and some may live as long as 20 years.

The disease has three phases.

During the first stage, a patient notices some forgetfulness, which can create anxiety or depression. Then, in the second stage, the forgetfulness intensifies into severe memory loss, particularly short-term memory. The third stage entails severe confusion and disorientation, with some patients experiencing hallucinations and paranoid delusions. They may become childlike, violent or demanding. At this point, they are often unable to take care of themselves, needing full-time caretakers or placement in a nursing home.

Alzheimer's can be hard to diagnose. Similar symptoms can be caused by a variety of physical diseases, including a tumor, strokes, hypothyroidism, pernicious anemia or Vitamin B-12 deficiencies.

The disorder's most distinguishing characteristic is the presence of rock-hard plaques and tangles in the brain, through which a definitive diagnosis can be made after death.

Times staff writer David Lauter and wire services contributed to this story.

Reagan's Letter

Text of letter written by former President Ronald Reagan announcing he has Alzheimer's disease:

"My Fellow Americans,

"I have recently been told that I am one of the millions of Americans who will be afflicted with Alzheimer's Disease.

"Upon learning this news, Nancy and I had to decide whether as private citizens we would keep this a private matter or whether we would make this news known in a public way.

"In the past Nancy suffered from breast cancer and I had my cancer surgeries. We found through our open disclosures we were able to raise public awareness. We

Los Angeles Times, November 6, 1994

were happy that as a result many more people underwent testing.

"They were treated in early stages and able to return to normal, healthy lives.

"So now, we feel it is important to share it with you. In opening our hearts, we hope this might promote greater awareness of this condition. Perhaps it will encourage a clearer understanding of the individuals and families who are affected by it.

"At the moment I feel just fine. I intend to live the remainder of the years God gives me on this earth doing the things I have always done. I will continue to share life's journey with my beloved Nancy and my family. I plan to enjoy the great outdoors and stay in touch with my friends and supporters.

"Unfortunately, as Alzheimer's Disease progresses, the family often bears a heavy burden. I only wish there was some way I could spare Nancy from this painful experience. When the time comes I am confident that with your help she will face it with faith and courage.

"In closing let me thank you, the American people for giving me the great honor of allowing me to serve as your President. When the Lord calls me home, whenever that may be, I will leave with the greatest love for this country of ours and eternal optimism for its future.

"I now begin the journey that will lead me into the sunset of my life. I know that for America there will always be a bright dawn ahead.

"Thank you, my friends. May God always bless you.

"Sincerely, Ronald Reagan."

GRAPHIC: Photo, COLOR, (Southland Edition, A1) Ex-President Reagan in 1991. ANNE CUSACK / Los Angeles Times; Photo, Ronald Reagan attended the funeral of Richard Nixon along with the current and former presidents in April. MARK BOSTER / Los Angeles Times; Photo, (Southland Edition, A25) Ex-President Reagan

LANGUAGE: ENGLISH

LOAD-DATE: November 7, 1994

420TH STORY of Level 1 printed in FULL format.

Copyright 1994 Newsweek
Newsweek

November 14, 1994 , UNITED STATES EDITION

SECTION: NATIONAL AFFAIRS; Ronald Reagan; Pg. 38

LENGTH: 548 words

HEADLINE: 'I Wish I Could Spare Nancy'

BYLINE: TOM MORGANTHAU

HIGHLIGHT:
Facing Alzheimer's disease

BODY:

THE LETTER, WRITTEN IN THE FORMER president's own hand, was calm and positive despite the grim news: Ronald Reagan, now 88, is suffering from the early stages of Alzheimer's disease. "At the moment I feel just fine," Reagan wrote last week. "I intend to live the remainder of the years God gives me on this earth doing the things I have always done. . . . Unfortunately, as Alzheimer's disease progresses, the family often bears a heavy burden. I only wish there was some way I could spare Nancy from this painful experience." Then he summed up: "I now begin the journey that will lead me into the sunset of my life. I know that for America there will always be a bright dawn ahead. Thank you, my friends. May God always bless you."

Who could say it better? With a grace and gallantry that recalled his quips after he was shot by John Hinckley in 1981, Reagan announced his illness to a public that, whatever it now thinks about his presidency, still admires his easygoing charm. But there was no hint of his self-deprecating humor -- and no mistaking the valedictory tone of his communique. Reagan seemed to be saying farewell: Alzheimer's is progressive, irreversible and largely resistant to current therapies. Over time, it causes memory loss, severe personality changes and, finally, dementia. The disease, still mostly a medical and neurological mystery, afflicts up to 25 percent of all Americans in their 80s. Reagan's doctors, in a letter released with his, seemed confident of their diagnosis, though they gave no explanation of the tests or procedures they used to reach it. Still, experts say that with good care, Reagan should be able to function normally for several more years and continue to enjoy his retirement.

He has clearly been doing that. After maintaining a decorous, ex-presidential silence for almost six years, Reagan emerged for a \$ 1,000-a-seat GOP fund-raiser in Washington last February. Margaret Thatcher was there; so, of course, was Nancy. Reagan wowed the nostalgic crowd with a genial mix of conservative boilerplate and partisan gibes at Bill Clinton, whom he accused of "grand larceny" by appropriating Republican themes. Predictably, he got the crowd cheering with another of his trademark jokes. "With all that's going on right now, I'm afraid I'm not going to run for president in '96," he said. Then -- skipping the requisite beat -- he said, "However, I have not ruled out the possibility of running again in 2000."

Newsweek, November 14, 1994

He broke his silence again in March -- this time with a more serious message that was plainly written with an eye to his place in history. The target was Oliver North, then beginning his successful, hard-right campaign for the GOP Senate nomination in Virginia. In a public letter to former senator Paul Laxalt, an old ally, Reagan said he was "pretty steamed" at North's "false statements" about the Iran-contra affair. He insisted once again that he "did not know anything" about the inner workings of the scandal and had never instructed North (or anyone else) to mislead Congress. Historians will someday judge whether Reagan was telling the whole truth or not -- but for now, given the sad inevitability of his condition, the mystery that blighted his presidency must stand unsolved.

GRAPHIC: Picture, Into the sunset: In California earlier this year, JOHN FICARA
-- NEWSWEEK

LANGUAGE: ENGLISH

LOAD-DATE: November 17, 1994

391ST STORY of Level 1 printed in FULL format.

Copyright 1994 The Time Inc. Magazine Company
People

November 21, 1994

SECTION: UP FRONT; Pg. 60

LENGTH: 1401 words

HEADLINE: INTO THE TWILIGHT;

With grace and courage, Ronald Reagan faces one final foe: Alzheimer's disease

BYLINE: BILL HEWITT

LYNDA WRIGHT and LYNDON STAMBLER in Los Angeles, ROCHELLE JONES and ALICIA
BROOKS in Washington, and bureau reports

BODY:

ON SUNDAY, NOV. 6, RONALD REAGAN AND HIS wife, Nancy, enjoyed a routine day at their ranch in California's Santa Ynez Mountains. The former President went horseback riding and chopped some wood. As has often been the case of late, the couple had no visitors and that night had a quiet dinner alone.

If there was anything remarkable about that Sunday, it was in its contrast to the commotion the 83-year-old former President had caused the previous day. In a touching, handwritten note released by his office in Los Angeles, Reagan had told the American people that while he felt "fine" now, he had been diagnosed with Alzheimer's disease, the incurable brain disorder that gradually -- but relentlessly -- renders its victims incapacitated and eventually results in their deaths.

It was vintage Reagan to deal forthrightly once again with a medical problem, just as he had done with all the lesser ailments that had plagued him over the years, including skin and colon cancer and an enlarged prostate. In the wake of the announcement, his office and presidential library were flooded with thousands of calls from well-wishers -- from Barbara Walters to Merv Griffin -- who took the opportunity to praise his bravery. "What he did was enormously courageous and selfless and typical of him," says old friend Charlton Heston.

Amid the outpouring of goodwill, there was the prospect that Reagan's candor might demystify a terrifying disease in much the same way that former First Lady Betty Ford had helped bring alcoholism and breast cancer out of the shadows and into the realm of public discourse. And painful as it was, the former First Couple clearly felt a sense of relief at finally disclosing the truth. When Nancy's former press secretary Elaine Crispen, who had no advance warning, learned of the President's announcement, she immediately called her ex-boss to offer support. "I almost felt like I was making a condolence call, but once she and I got beyond that and she assured me that he was feeling fine, we even laughed," says Crispen. "We started sharing stories, and she was in pretty good spirits."

It is unclear exactly when the Reagan family began to notice signs of deterioration in the former President's memory. Certainly during his Presidency,

People, November 21, 1994

and especially in the last several years of his Administration, there were widespread reports of his inattentiveness during meetings and forgetfulness about policy details. All the same, most aides and many outside observers simply chalked up those lapses to his somewhat casual style of governing. "There were always gaps," says Reagan biographer Lou Cannon. "There were some days when he was sharp, some days when he wasn't."

Not long after he left office, though, there were some disturbing episodes. When he met Bill Clinton shortly after the 1992 election, he stopped mid-sentence and looked angry. "He said, 'I forgot,' " Clinton recalled. "He said, 'I lost my memory on that and it really makes me mad.' "

In January 1993, at a party to celebrate his 82nd birthday, Reagan gave a notably unsteady performance during his speech to the assembled guests, including Jimmy Stewart and former British Prime Minister Margaret Thatcher. "At one point he forgot where he was in his [written] speech," says Paul Keeley, an actor who was moonlighting as a waiter at the Simi Valley event. "He looked up and seemed confused. Then he went back to the beginning and started reading from the top and didn't realize he'd done it." The room fell silent. "He went on to ad-lib some jokes," says Keeley. "People were very polite, but everyone was very aware of what was going on."

About a year ago, Reagan reportedly went to the Mayo Clinic in Rochester, Minn., for a series of tests. The report came back that he was in the early stages of Alzheimer's. The decision was made to keep the diagnosis confidential, within Reagan's immediate family. Son Michael, 49, host of a syndicated radio talk show in Los Angeles, says that shortly after learning about the disease, his stepmother circulated a copy of *The 36-Hour Day*, a book that deals with the issue of caring for Alzheimer's victims.

As a manual, says Michael, the book proved enormously useful. "The last thing you want to do as a family member is misinterpret what is going on and treat the person like they're stupid or yell at them for not doing this or forgetting that when, indeed, they have a disease they have no control over," he says. "So we let him tell his stories. If he forgot something, then he would come back to it. You just have to be patient."

Reagan's daughter Maureen, 53, who lives in Sacramento, and Ron Jr., 36, an aspiring actor, have also rallied to his side. Even daughter Patti, 42, who recently posed nude for *Playboy* and has had, at best, strained relations with her parents, got in touch. "She's had several conversations with her family about this," says a friend. "She says they've been very pleasant."

At times, associates say, the former President can be his hale old self. "Five or six months ago I had a perfectly normal conversation with him," says one former aide in Washington. "It was not the kind of conversation where he could have learned his responses, and he was fine." Still, in his increasingly rare public appearances, including the funeral of former President Richard Nixon last April, Reagan looked distressingly feeble to those who observed him up close. Ultimately, Reagan himself decided that he wanted to share the news of his affliction with the American people rather than let speculation about his condition continue to build -- as it did when he failed to campaign for Republican candidates this fall. Despite the somber nature of the announcement, Reagan managed to sound upbeat -- almost jaunty. "I now begin the journey that

People, November 21, 1994

will lead me into the sunset of my life," he wrote. "I know that for America there will always be a bright dawn ahead."

By starting that journey so candidly, Reagan may help banish much of the stigma that has long been associated with Alzheimer's. Often viewed as a psychiatric disorder by much of the public, Alzheimer's is in fact a neurological disease characterized by a deficiency in the brain of chemicals known as neurotransmitters, which allow brain cells to communicate with each other. When these cells stop communicating, says Dr. Zaven Khachaturian, director of the Office of Alzheimer's Disease Research at the National Institutes of Health in Bethesda, Md., the cells wither and eventually die. Although Alzheimer's can affect speech, personality and motor functions, the most conspicuous early symptoms usually involve memory loss. In the more advanced stages, that loss can be devastating. "You and I may forget where we parked the car, but an Alzheimer's patient can't remember if he drove that day," says Khachaturian. "He'll look at the car keys and forget what they're for."

In some cases, Alzheimer's patients have been frightened just by looking in the mirror. Because they have forgotten what their own faces look like, they believe there is a stranger in the room. Ultimately, the disease can completely disable patients by robbing them of the ability to feed or care for themselves. It usually leads to death eight to 10 years after it is diagnosed.

In the U.S., Alzheimer's afflicts some 4 million people. Though the disease is believed to be often inherited (Reagan's mother, Nelle, is thought to have suffered from Alzheimer's), it strikes all segments of the population. Among the many famous Americans who have suffered from Alzheimer's are actors Rita Hayworth, Dana Andrews and Edmond O'Brien, painters Norman Rockwell and Willem de Kooning and boxer Sugar Ray Robinson.

Researchers are hopeful that in the next few years an effective treatment for the disease will be developed. It will probably come too late to help the former President, but his family is determined to cherish the time they have with him while he is still reasonably healthy. Elaine Crispen says Nancy told her that Alzheimer's patients sometimes don't become debilitated for eight or nine years. "She mentioned that in that case, he would be 92 years old, and that would be wonderful," says Crispen. Michael says his daughter Ashley, 11, put it more simply when she was told of her grandfather's condition. "I'm going to love my grandpa," she said, "even if he doesn't know who I am."

GRAPHIC: Picture 1, Ronald Reagan's poignant battle descColor cover inset: Ronald Reagan waving., Fred Prouser/SIPA PRESS; Picture 2, CANDOR Stricken with Alzheimer's, Ronald Reagan embarks on "the journey . . . into the sunset of my life." descColor: Ronald Reagan - contents page., STANLEY TRETICK/SYGMA; Picture 3, Reagan seemed unsteady at Richard Nixon's funeral in April. "I only wish there was some way I could spare Nancy this painful experience," he said as he disclosed that he has Alzheimer's. descColor: Nancy Reagan leading Ronald Reagan by the hand., GARY CASKEY/SIPA PRESS; Picture 4, Nancy has helped the former President (with Margaret Thatcher) get through public events such as his 82nd-birthday bash in 1993. descColor: Margaret Thatcher, Ronald Reagan, Nancy Reagan in front of birthday cake., (c) LISA ROSE/GLOBE PHOTOS; Picture 5, At a California campaign rally in 1992, the former President took his ease with daughter Maureen, granddaughter Ashley, Nancy and son Michael. descColor: Maureen Reagan, Ashley Reagan, Nancy Reagan, Michael Reagan, Ronald Reagan sitting on the grass, others., (c) DOUGLAS BURROWS/GAMMA LIAISON; Picture 6, "I

People, November 21, 1994

always liked the fact that he was positive," said Bill Clinton of Reagan (in 1992). descColor: Ronald Reagan, holding jar of red, white and blue jelly beans, and Bill Clinton laughing together., J. SCOTT APPLEWHITE/AP
LANGUAGE: ENGLISH

LOAD-DATE: November 22, 1994

227TH STORY of Level 1 printed in FULL format.

Copyright 1995 The New York Times Company
The New York Times

March 5, 1995, Sunday, Late Edition - Final

SECTION: Section 1; Page 23; Column 1; National Desk

LENGTH: 202 words

HEADLINE: Nancy Reagan Talks Of Alzheimer's Trial

BYLINE: AP

DATELINE: WASHINGTON, March 4

BODY:

Nancy Reagan said today that former President Ronald Reagan had been doing fine since his Alzheimer's disease was diagnosed but that the mind-crippling illness was wrenching for her.

In an interview on CNN's "Larry King Weekend," Mrs. Reagan would not elaborate on her husband's physical condition, but she said that "there've been better" days.

The host, Larry King, asked whether Alzheimer's disease was harder on loved ones than patients. "That's true," Mrs. Reagan responded. And, reflecting on the joys of her life, she added, "You pay for everything, don't you?"

Mr. Reagan, 83, disclosed in November that he was in the early stages of Alzheimer's, an incurable neurological disorder that destroys the brain's memory cells.

Mrs. Reagan said she planned to film a public-service announcement to bring attention to the disease.

She spent the interview reviewing her husband's life through displays in his Presidential library in California. She also pointed out the couple's burial plot in Simi Valley, but, she said laughing, "I don't expect to jump in there any time soon."

She said her husband liked the site. "I think he'll be very happy there," she said. "I mean, the view is pretty."

LANGUAGE: ENGLISH

LOAD-DATE: March 5, 1995

203RD STORY of Level 1 printed in FULL format.

Copyright 1995 The Times Mirror Company
Los Angeles Times

March 23, 1995, Thursday, Home Edition

SECTION: Life & Style; Part E; Page 7; View Desk

LENGTH: 378 words

HEADLINE: NANCY REAGAN SPEAKS OUT FOR A GOOD CAUSE;
HEALTH: THE FORMER FIRST LADY'S PUBLIC SERVICE ANNOUNCEMENTS FOR THE ALZHEIMER'S
ASSN. ARE EXPECTED TO DRAMATICALLY INCREASE AWARENESS.

BYLINE: By TRACY JOHNSON, TIMES STAFF WRITER

BODY:

When former President Ronald Reagan announced that he had Alzheimer's disease in November, calls to the Alzheimer's Assn. increased by 150%. Today, when the organization releases several public service announcements with Nancy Reagan discussing the effects of the disease on families, officials expect the phones to ring off the hook.

"We think she can call attention to the issue with greater impact than anyone else can," said Kathryn Kane, senior vice president of communications for the association.

The former First Lady offered to do the public service announcements after experiencing the emotional devastation of Alzheimer's firsthand. She urges those faced with the problem to call the association for help.

"No one is immune from Alzheimer's disease," Reagan is quoted as saying in a press release explaining why she made the spots. "Families really need help to understand it and cope with it, emotionally and in many other ways."

America's awareness of the disease has increased significantly since Ronald Reagan's diagnosis. According to Kane, calls to the organization have remained so high that extra phone lines were hooked up and additional operators were hired. Nancy Reagan's message is especially important, said Kane, because families need to know that help is available.

"Family members don't always know what's going on," Kane said. "They end up taking care of this person that looks healthy but whose behavior has changed drastically. They don't realize that they need help themselves." Kane added that as many as 80% of Alzheimer's caregivers suffer stress-related illnesses.

*

Nearly 4 million Americans are afflicted by this brain disease that affects memory and the ability to think and make judgments. People who have Alzheimer's often don't know who they are and can't function in daily life.

The public service announcements are sponsored by the Alzheimer's Assn. and

Los Angeles Times, March 23, 1995

the National Institute on Aging, and produced by KTTV/FOX 11 Los Angeles.

The Alzheimer's Assn. is a nonprofit organization dedicated to prevention research and providing assistance to families. The association has more than 200 chapters in all 50 states and offers a wide range of programs and services. For more information, call (800) 272-3900.

LANGUAGE: ENGLISH

LOAD-DATE: March 29, 1995

167TH STORY of Level 1 printed in FULL format.

Copyright 1995 The Washington Post
The Washington Post

June 08, 1995, Thursday, Final Edition

SECTION: STYLE; Pg. D01

LENGTH: 1316 words

HEADLINE: Reagan's Cloudy Days; Friends Say He's Fit, At Times Forgetful

BYLINE: Elisabeth Bumiller, Special to The Washington Post

DATELINE: NEW YORK

BODY:

Seven months after Ronald Reagan announced he was suffering from Alzheimer's disease, an incurable neurological disorder that steadily destroys memory, friends and associates of the 84-year-old former president say he is happy, physically vigorous but mentally on a gentle roller coaster of good and bad days.

In April, a distressed Nancy Reagan told a friend that her husband had recently seen the White House on television and on that particular day, the friend said, Ronald Reagan could not remember ever having lived there.

But a former staff member, Frederick J. Ryan Jr., said this week that when he saw Reagan in mid-May in Los Angeles, the former chief executive was well aware of his years in Washington. "He had no problem at all recalling his presidency," Ryan said.

Alzheimer's specialists, who emphasized they were not in any way commenting on Ronald Reagan's case in particular, said a pattern of forgetting something one day and remembering it the next is typical of the disorder. "We've come to realize that the chemistry of the brain can change a lot from day to day, even though overall the course of the disease is steadily downhill," said Marilyn Albert, the director of gerontology research at Massachusetts General Hospital and an associate professor at Harvard Medical School who has studied Alzheimer's for 18 years.

"Alzheimer's is a disease, like any other disease -- cancer, heart disease, whatever," Nancy Reagan said in a short speech in New York on Monday night. "But unfortunately, for far too long, people have been embarrassed and self-conscious about admitting it. As time goes by, and people live longer lives, this becomes an enormous problem."

Mrs. Reagan closed her remarks at the Hotel Pierre by saying that Alzheimer's is a "really very cruel disease" and that the families of victims need support and understanding.

"Because, for the caregiver," she said, as her eyes reddened and her voice broke, "it's a long goodbye."

The Washington Post, June 08, 1995

In recent months, poignant stories about Ronald Reagan have been circulating among his friends. Six weeks ago, Earle and Marian Jorgenson were the hosts of a dinner for the Reagans at Matteo's, a popular celebrity restaurant in Los Angeles. Larry Cullen, the restaurant's manager, said the room broke into applause as the former president was leaving, which has always happened when the Reagans dined there over the years. But on this night Reagan was not aware that the applause was for him. Nancy Reagan gently guided him to turn and accept the ovation, at which point Reagan jumped to attention and, with a big smile, saluted the room. His friends were in tears.

Reagan announced in November 1994 that he was in the early stages of Alzheimer's, and at the time released a handwritten letter that was applauded for its frankness and courage. "I now begin the journey that will lead me into the sunset of my life," he wrote. "I know that for America there will always be a bright dawn ahead."

The average duration of Alzheimer's disease is seven to 10 years, and it eventually leads to death. There are an estimated 4 million people suffering from Alzheimer's in the United States, most of them older than 65. Since the announcement, the Reagans have received 50,000 pieces of mail from people in the United States and overseas.

"I want to let other victims and their families know they are not alone in their struggle," Nancy Reagan said in her speech in New York, where she accepted an award from the Harvard Mahoney Neuroscience Institute. The award recognized the Reagans for helping to increase public awareness of neurodegenerative diseases.

Friends say Ronald Reagan continues to go to his office from 10 a.m. to 3 p.m. every day in Los Angeles, where he meets with visitors, signs books and photographs for supporters and handles paperwork. He exercises every morning with a personal trainer at a Los Angeles gym, plays golf once a week, attends church on Sunday, chops wood at his ranch and goes to small dinner parties with longtime friends. Those who have seen him in the past year say he looks fit and healthy, and that he is not rapidly deteriorating, as sometimes happens with Alzheimer's patients.

Brian Mulroney, the former prime minister of Canada, a friend of the Reagans and Nancy Reagan's dinner partner at the awards ceremony in New York, said he last saw the former president 10 months ago. "He was like he always was -- vigorous and funny," Mulroney said. "I noticed things, you know, but my own father died when he was quite young, so I thought this was just a person getting old. It was nothing like, 'Oh my God, Ron is sick.' It's just a gentle progression."

Another family friend said this week that Reagan seems more dependent than ever on his wife. "When I talk to her now on the phone, he is in the background asking questions every 30 seconds," the friend said. "What used to be 30-minute conversations with her are now five."

Other friends say they call Mrs. Reagan to keep her spirits up, but hesitate to badger her with questions, and that in any case she does not like to talk about her husband's disease in much detail. "I think Nancy appreciates the phone

The Washington Post, June 08, 1995

calls and messages," said Nancy Reynolds, an old Reagan friend now living in Santa Fe, N.M. "But to call her every week and ask 'What's going on? What's the progress?' -- that would drive me nuts."

"Everyone has encouraged her to keep real busy," said Elaine Crispen, Nancy Reagan's former press secretary. "When the story first came out, I told her, 'You cannot become imprisoned by this,' and she said, 'I know that -- but I have to be sure there is someone with him I can absolutely rely on.' "

In March, Mrs. Reagan made a trip to Washington to deliver her anti-drug message before a House subcommittee, and said at the time that it was difficult to leave her husband at home. During their eight years in the White House, the Reagans most often traveled together; when she went to London by herself to attend the wedding of Prince Charles and Diana Spencer in 1981, an aide said the first lady was so upset about leaving the president for a week that she cried the night before. This week Mrs. Reagan was in New York not only to accept the Harvard award but also to sign copies of "Ronald Reagan: The Wisdom and Humor of the Great Communicator" at Barnes & Noble on Fifth Avenue. Ryan, Reagan's chief of staff in California until the end of last year, is the editor of the book.

In January, Edmund Morris, Reagan's biographer, wrote in the New Yorker that, six months earlier, Reagan had stopped recognizing him. "Now I no longer recognize him," wrote Morris, who has been working with Reagan on the book for nearly a decade. "For all the intimate familiarity of that face and body, for all the willingness with which he showed me his framed photographs, his jelly bean jar, and his view of the Hollywood Hills, I did not feel his presence beside me, only his absence."

Reagan no longer makes public appearances, but a friend said this is not specifically because of the symptoms of Alzheimer's. The friend said the bigger problem, for now, is that media scrutiny of Reagan's health overshadows any other message the former president may be trying to get across.

"He realizes that whatever he tries to do now, the story will be Alzheimer's," the friend said. "And he realizes that at some point, the disease will prevent him from making public appearances -- and he doesn't want to push it to the last bit."

In the meantime, friends and family have formed a cocoon around Ronald Reagan.

"He is in excellent physical shape and he enjoys immensely the time he gets to spend with his family," said Dennis Revell, the husband of Maureen Reagan, Ronald Reagan's eldest daughter.

"He looks absolutely wonderful -- better than he's ever looked in his life," said Marian Jorgenson.

GRAPHIC: Photo, reuter, Nancy Reagan in New York: "Alzheimer's is a disease, like any other" -- and also a "very cruel" one. Nancy Reagan accepts an award Monday in New York from Daniel Tosteson of Harvard Medical School for increasing public awareness of Alzheimer's.

LANGUAGE: ENGLISH

LOAD-DATE: June 08, 1995

12TH STORY of Level 1 printed in FULL format.

Copyright 1996 Gannett Company, Inc.
USA TODAY

February 5, 1996, Monday, FINAL EDITION

SECTION: NEWS; Pg. 1A

LENGTH: 1841 words

HEADLINE: REAGAN AT 85 // 'The Gipper' still upbeat, say friends

BYLINE: Maria Puente; Sally Ann Stewart

BODY:

He walked with the same upright posture, flashed the same sunny smile and gave the same crisp wave.

Seven years after leaving office, the videotaped image of Ronald Reagan walking to his office unassisted last weekend was enough to dispel the worst rumors about his health.

But his glasses, slow gait and a puzzled look hinted at the changes brought on by Alzheimer's disease that have transformed the life of the 40th president.

When Reagan turns 85 on Tuesday, a who's-who ranging from Bob Hope and Charlton Heston to Colin Powell and Newt Gingrich will gather to celebrate. Reagan, too uncomfortable now to attend big public events, won't be there.

But his influence on Republicans lives on - in the praise of GOP congressional freshmen as well as on the campaign trail, where all the GOP candidates claim to be the true heir to Reagan's political legacy.

"He's as well loved as any person in this country," says Lyn Nofziger, who first worked for Reagan as governor of California in 1966. "With some people, as they fade into the twilight their reputations diminish. For some people, their reputations keep growing, and Reagan is one of those guys."

The party is at Chasen's, the Los Angeles eatery that's opening again for the celebration after closing last year. Ronald Reagan proposed to Nancy there. It's also where they planned their wedding and where she was the host of his 60th and 80th birthday parties.

There won't be a birthday cake. Without her husband there to blow out the candles, Nancy Reagan thinks it won't be the same.

"It's going to be kind of sad for (the family)," says Maureen, 55, Reagan's daughter from his first marriage to Jane Wyman. "But I'm looking forward to it. It's a chance to reminisce and smile."

Maureen Reagan says she hopes people will remember her father as "more than just the disease that caught him in his older years."

USA TODAY, February 5, 1996

"I want people to remember Ronald Reagan the lifeguard in Dixon, Ill., or the movie actor in Hollywood, or the governor or the president. He touched so many people in so many different ways.

"Last summer, we were sitting out by the pool and when I looked at him, I still saw this gorgeous, tanned Adonis who used to push me into the pool with his hip to make sure I could swim."

The birthday party started out as an indoor "intimate" dinner for 200 Reagan friends. But demand for tickets was so strong, more than 400 people now are expected to attend the \$ 1,000-a-plate fund-raiser for the Reagan Presidential Foundation.

Dinner will include Reagan favorites: Chasen's chili, chicken pot pie and, for dessert, a snowball - ice cream rolled in coconut with chocolate sauce.

"They used to sit around here and talk about Chasen's chicken pot pies all the time, so I'm looking forward to seeing what this is after all these years," says Sheila Tate, then-first lady Nancy Reagan's press secretary.

Other guests include former president Gerald Ford and California Gov. Pete Wilson. Merv Griffin will be master of ceremonies and Johnny Mathis will sing.

Other, less well-known fans, more than 1,000 so far, have had a chance to send birthday greetings, and \$ 85 donation checks. By midday Sunday, about 200 people had arrived at the Reagan Library in Simi Valley to sign a giant birthday banner.

One message from Joe and Nancy Balestrain: "Happy Birthday to the greatest living American."

Another from Karen Poltrock: "Happy 85th. God bless you. You saved our country."

The long-held affection for Reagan gathered strength in November 1994, after he released a handwritten farewell letter disclosing that he was one of 4 million Americans diagnosed with Alzheimer's disease.

The Reagans and the library have been deluged with cards and letters since, about 1,000 a week. So far, 100,000 pieces of correspondence have come in from around the world.

"Americans remember Ronald Reagan so fondly because of the kindness and decency which were his hallmarks as president," says former president George Bush, Reagan's vice president. "The American people, political friends and foes alike sensed this and loved him for it."

Marlin Fitzwater, press secretary for Reagan and Bush, says even opponents couldn't resist his charm.

Whatever the state of his memory, Reagan remains in good physical health, and friends say he hasn't lost his upbeat personality.

"He still has the same optimism, the same warmth and response to people, the same easygoing manner," says Fred Ryan, Reagan's chief of staff for six years

USA TODAY, February 5, 1996

after leaving office.

"I think the Gipper would say, 'I don't want anyone feeling sorry for me,' " says former Reagan speechwriter Ken Khachigian.

Reagan's days

Reagan works out with weights and a personal trainer every morning at a private gym. He arrives at his penthouse-floor office in a Century City neighborhood, about 10 minutes from his home in Bel Air, just before 10 a.m. He stays until around 2 p.m., reading mail, signing books or autograph requests, and meeting with friends.

One day a Boy Scout troop might come by. On another day, Air Force pilot Scott O'Grady, shot down in Bosnia and rescued six days later, stops in to meet Reagan.

"He works with the staff to schedule time to meet all sorts of people, former staff members, supporters, government officials, students, visitors from Dixon and individuals who have written him letters which have touched him in a special way," says Joanne Drake, his current chief of staff.

Other old friends and associates say they hesitate to ask to visit him.

"It would be too painful," says Stu Spencer, a longtime adviser. "From what I hear, he remembers you one day and not the next. I don't know if I could handle it."

Once or twice a week, Reagan leaves the office early to hit a bucket of golf balls at the Los Angeles Country Club and maybe swim a few laps.

He usually plays nine holes at least once a week with friends such as actor Tom Selleck or publishing magnate Walter Annenberg.

Head golf pro James Schaeffer says Reagan usually shoots in the 50s for nine holes of golf.

"I've given him a couple of golf lessons," says Schaeffer. "He's very good, especially for his age."

Besides attending church at Bel Air Presbyterian, the Reagans sometimes go to the Reagan Library. He has been known to turn up unannounced, tap an astonished guide on the shoulder and lead a tour himself.

Protected by Nancy

Nancy Reagan occasionally goes out to dinner with old friends. But generally the two live quiet, private lives. As she was during the White House years, Nancy Reagan is fiercely protective and tries to preserve his image by allowing no pictures of him.

Gossip columnist Aileen Mehle, a friend of Nancy Reagan who writes under the name Suzy, says the former first lady was greatly touched by the outpouring of sympathy for her husband.

USA TODAY, February 5, 1996

Like other friends, she says Nancy Reagan is coping with the strain of her husband's illness but saddened by the loss of their mutual memories.

"You look at her face and see her sad eyes, but she's stalwart and courageous and going about it the way she should, because she knows she can't just fall in a heap," Mehle says. "It's the most terrible thing to see someone you love deteriorate before your eyes and nothing to be done about it."

One consequence of Reagan's illness is that his once-divided family has rallied around. Daughter Patti Davis, long a family rebel, has reconciled with her mother and wrote a book to her father. She lives in New York and visits once a month.

Michael, Reagan's son from his first marriage and now a radio talk-show host, lives in Los Angeles and spent Christmas with the Reagans.

Younger son, Ron Jr., lives in Seattle.

"There are certain hardships in life where all you can do is be there," says Maureen Reagan, who lives in Sacramento and visits regularly. "You can't make it better, you can just be there. I guess this is one of those times."

It is unclear when Reagan first developed Alzheimer's disease. There's evidence the disease may be inherited. Reagan's mother suffered dementia before she died.

Researchers say the disease may be present in the brain 30 or more years before symptoms become noticeable. In Reagan's case, some say signs were there as early as his second term in the White House, 1984-1988.

In March 1990, 14 months after he left office, Reagan was mostly lucid during a wide-ranging interview with USA TODAY. But near the end of the interview, Reagan had a hard time responding to an off-the-cuff question about his plans to celebrate one of his favorite holidays - St. Patrick's Day.

There was no Reagan quip. Instead, he fumbled around on his desk for his calendar. After a few awkward moments, he reached over and held up a green tie sitting on the edge of his desk.

"The mayor of Dublin sent this to me," he said.

After announcing his diagnosis, the Reagans joined forces with the national Alzheimer's Association to establish the Ronald and Nancy Reagan Research Institute, which tries to connect researchers around the world in the search for treatment, prevention and cures.

Zaven Khachaturian, director of the institute, says the Reagans' openness about his diagnosis was a "tremendous" signal that helps destigmatize the disease.

"It's a positive message to the public that this is not a hopeless disease," Khachaturian says.

And Nancy Reagan appeared in a series of public service announcements on

USA TODAY, February 5, 1996

behalf of the association.

Maureen Reagan says Alzheimer's disease can teach hard lessons to families: "All we can do is live our lives the best we can every day because heaven only knows how long we have or what will happen tomorrow. Life is always too short."

A birthday salute from the president

The following is an excerpt from President Clinton's birthday tribute to Ronald Reagan in the February issue of Vanity Fair:

There is a room on the second floor of the White House called the Yellow Oval Room, and I gather that this remains President Reagan's favorite place in the great house that we have both been privileged to inhabit. . . . No one room could better represent what Americans love about President Reagan. We remember the sunniness of his temperament during eight years in office: The room's color gives it a steady glow during clear days and stormy ones alike. Its view is expansive. From it, you can see the Jefferson Memorial, the Washington Monument, the broad Potomac, even the foothills of Virginia. . . .

As President, Ronald Reagan made us feel that he genuinely liked Americans. I imagine that what he enjoyed most about his room is that the view is not limited to the monuments.

From its window, you can also see families walking along the Mall, people driving to work along Constitution Avenue, children playing softball on the Ellipse. . . .

As he turns 85, President Reagan is still very much in our minds. And though he's been back in California for a few years now, I think a little of his hopeful exuberance stayed behind in the Yellow Oval Room to cheer his fellow citizens - indoors and out.

GRAPHIC: PHOTO, color, CNN; PHOTO, color, AP; PHOTO, b/w, Robert Hanashiro, USA TODAY

LANGUAGE: ENGLISH

LOAD-DATE: February 06, 1996

58TH STORY of Level 1 printed in FULL format.

Copyright 1995 The Times Mirror Company
Los Angeles Times

June 11, 1995, Sunday, Bulldog Edition

SECTION: Part A; Page 1; Advance Desk

LENGTH: 1243 words

HEADLINE: EARLY ALZHEIMER'S DIAGNOSIS LETS ITS VICTIMS CALL DEVIL BY NAME;
DISEASE: ONCE-FULL LIVES SLIP AWAY, AND KNOWING WHY ISN'T ALWAYS COMFORT. BUT
SUPPORT GROUPS CAN HELP PATIENTS RETAIN THEIR DIGNITY.

BYLINE: By ANDREA HAMILTON, ASSOCIATED PRESS

DATELINE: NEW YORK

BODY:

Frank MacShane opens the door, bewildered but gracious. He doesn't know who his visitor is, but ushers her in anyway and immediately asks for help.

He's misplaced his wallet, and he has a handful of cash and credit cards he needs to put away. The wallet is found 10 minutes later in the bedroom. He tries but he cannot insert the contents, so the visitor helps.

That settled, MacShane, 67, pauses to smooth his charcoal-gray slacks, adjust his blazer and ask the visitor to remind him what she's doing in his home. And who is she, he inquires, in the deep professorial voice that discoursed on literature and writing for 25 years at Columbia University.

She is there to discuss MacShane's life and how Alzheimer's disease is slowly overtaking it.

Of course, he says. MacShane's discomfort recedes as he settles into a chair and proceeds to talk engagingly about his years as a professor and the books he has written, including biographies of Raymond Chandler and John O'Hara.

He pauses frequently in mid-sentence to grope for the words that he says run around corners and hide from him. "It's this damned disease, you know," he says.

More and more Alzheimer's victims are like MacShane, people who fall into a relatively new category called "early diagnosis" who are very much aware they are becoming shells of their former selves.

In the past, senility was a catch-all term used to describe older people who had memory and thinking problems; when they could no longer take care of themselves, many were shipped off to nursing homes. But Alzheimer's is a very specific disease, caused by lesions on the brain.

Only an autopsy can give 100% confirmation of the disease, but increasingly sensitive tests can diagnose it with 95% accuracy. It is because of these tests, and greater awareness of Alzheimer's, that people are being diagnosed long

Los Angeles Times, June 11, 1995

before they are incompetent and need 24-hour care.

The disease respects no rank or station. Former President Ronald Reagan announced last November that he has been diagnosed with the disease.

When the Alzheimer's Assn. was founded 15 years ago, its primary mission was to help relatives make sense of what was happening to their loved ones. Support groups for care-givers flourished.

But with early diagnosis, many of the 4 million victims across the nation began asking their own questions, and now support groups for them are burgeoning.

"Many of these people can't work anymore. Friends have disappeared. Maybe they've begun to feel like a nuisance around the house. Other people in a support group understand this," said Robyn Yale of San Francisco, a clinical social worker who has written two training manuals for patient support groups.

An Alzheimer's support group in Manhattan declined to allow a visitor to listen in, but two members, MacShane and Cal Stadlen, agreed to be interviewed individually.

According to figures from the Alzheimer's Assn., 5.8 million Americans over the age of 65 will have the disease in 10 years, and 14 million in the year 2050.

With early diagnosis, many people live eight to 20 years with the disease, and are mildly afflicted for some time.

For these people, there is still plenty of living to be done, and support groups can inspire them to press on, said Anita Sanborn, executive director of the Denver-based Rocky Mountain chapter of the Alzheimer's Assn.

MacShane and Stadlen see their support group as a refuge, a place where they are learning to lose their minds with dignity and humor.

Stadlen, an elfin man with a white goatee, looks much younger than his 80 years. He can't remember what he did yesterday. But he remembers the house he lived in as a little boy. It was in Coney Island, on Mermaid Avenue, and the shower was out back in a shed.

Stadlen has accomplished a lot since then. He's been married for 54 years. He's had a career producing television commercials, traveled the world, designed and built two homes. He was a sailor and a photographer.

But this once-full life is nearly empty now.

Stadlen doesn't know what day it is when he wakes up in the morning. He has trouble putting a key in a lock or opening a can. He once was one of the enviable people who filled in the Sunday crossword puzzle in ink. Now, he is stymied by the simplest words.

He recently forgot where he was going when he left his co-op apartment in Chelsea, so he rarely ventures out by himself anymore. When he does, he carries a note explaining what he's supposed to be doing.

Los Angeles Times, June 11, 1995

"The world hasn't shrunk. My role in it has," Stadlen said. "Suddenly, there is nothing."

His wife, Florence, said the support group helps fill this void, so much so that her husband's week has come to be defined by the meeting.

The groups vary across the country. The focus of the Manhattan group is sharing sadness and trying to come to terms with the disease. Others are forums for socializing, learning how to establish routines to make life easier or discussing plans for the future, including living wills.

"It was quite a relief to find that the other people in the group weren't a bunch of morons, as I sometimes consider myself to be," Stadlen said. "They are lovely people, even in their illness."

Rea Kahn, support group coordinator for the Alzheimer's Assn. New York City chapter, has watched many patients approach groups with trepidation.

"There is a huge sense of loss, many fears," she said, "but then they come here and realize they are not alone. They can let down their guard."

That's comforting for Stadlen and MacShane, but not for MacShane's only child, Nicholas. For more than three years, he has mourned as he has watched his father decline.

At first, there were jokes about his father being an absent-minded professor. His father would say he was too busy thinking about weighty matters to remember names or dates.

But then he couldn't tell time. He couldn't tell the difference between \$5 and \$500, and he was practically giving money away. Next, he started throwing pots and pans away after he cooked, and calling Nicholas to say he had lost his black poodle, Lily, who always turned out to be at MacShane's side. Nicholas finally persuaded his father to allow a housekeeper in eight hours a day, and now he hopes he will relent and let the woman, named Rita, move in. But there is little comfort for the 27-year-old son in this arrangement.

"He's become a prisoner of his own mind. And I am the son who is forced to hire the warden to follow him around and keep him in line," Nicholas said.

His father has talked about suicide, but lately has begun latching onto illusions for hope.

"He thinks, 'If I can just get rid of Rita, I'll be cured. If I could just start writing again, I'll be fine.' "

These days, Frank MacShane says a good day is when he's with his support group. "I have the feeling that life is OK. Nobody's cheering, but at least it's OK," he said. "Underneath all of us, there is a lot of angst, and sometimes we're willing to say what's going on, to tell the truth. We have fears, you know. We're all afraid the day will come when they have to put us in a box, or whatever they do with people who can't think or speak anymore."

As his visitor prepares to depart, MacShane asks for instructions on how to

Los Angeles Times, June 11, 1995

turn on the radio in case he wants to listen to it in the evening.

There's a big red on-off button and he punches it a couple of times.

"Well," he says with a doubtful smile, "that looks simple enough."

GRAPHIC: Photo, Wife Florence stands behind Cal Stadlen, who can't remember what he did yesterday but can remember the house he lived in as a boy. Associated Press

LANGUAGE: ENGLISH

LOAD-DATE: June 12, 1995

National Institute on Aging

Progress Report on Alzheimer's Disease, 1995

Contents

- ☐ Introduction
- ☐ Structure and Function of the Brain
- ☐ Changes in the Brain in Alzheimer's Disease
- ☐ Advances in Identifying Risk Factors for Alzheimer's Disease
- ☐ Advances in Diagnosing Alzheimer's Disease
- ☐ Advances in Treating and Preventing Alzheimer's Disease
- ☐ Research Conducted by Other NIH Institutes
- ☐ Outlook
- ☐ Full-Text ASCII Version



Home Page

Introduction

Alzheimer's disease (AD) is the most common cause of dementia, or mental deterioration, among people age 65 and older. A slowly degenerative brain disease, AD is marked by changes in behavior and personality and by an irreversible decline in intellectual abilities. It impairs thinking, memory, and judgment, advancing in stages that range from mild forgetfulness to severe dementia. The course of the disease varies from person to person, as does the rate of decline. The average duration of AD is from 4 to 8 years.

People with this disease may forget how to do simple tasks, like brushing their teeth or combing their hair. Often, they are unable to think clearly or remember the right names of familiar objects or people. Eventually, they become completely dependent on others for their care.

Risk for AD increases with advancing age. After age 65, the percentage of people who suffer from AD or other dementias doubles with every decade of life. However, AD is not a part of normal aging. AD and other dementing disorders of old age are caused by specific diseases. Without disease, the human brain continues to function well, often into the tenth decade of life.

Prevalence and Costs of Alzheimer's Disease

Currently, an estimated 4 million Americans suffer from AD. In addition, the lives of countless caregivers are affected by this devastating illness. Families experience emotional, physical, and financial stress. They watch their loved ones become increasingly forgetful, agitated, and confused. Many caregivers, most of

them women, juggle child care and jobs while caring at home for relatives with AD who cannot function on their own. As the disease progresses and the abilities of people with AD steadily decline, family members face painful decisions about the long-term care of their loved ones.

Moreover, AD puts a heavy economic burden on society. A recent study estimated that the cost of caring for one person with AD is more than \$47,000 a year, whether the patient lives at home or in a nursing home. For a disease that can range in duration from 2 to 20 years, the overall costs of AD to families and to society are staggering.

Other factors in our changing society compound the problem of AD. Life expectancy has been increasing since the turn of the last century. During the past three decades, improvements in public health measures, diet, and health behavior have brought about dramatic demographic changes, including a lower birthrate. Thus, today in most industrialized countries, the 85+ age group is the fastest growing segment of the population. The challenge of paying for health care for this population has yet to be tackled.

In light of these issues, AD, which primarily affects older people, represents a major health concern and expense for the United States. Until researchers find a way to cure or prevent AD, the number of people living to very old age (85+) and at risk for AD will continue to increase dramatically. Providing and financing the care of a growing older population present special challenges for our health care system.

Research Directions

AD research falls into three broad, overlapping areas of emphasis: cause(s)/risk factors, diagnosis, and treatment/caregiving. Research into the basic neurobiology of aging is critical to understanding what goes wrong in the brain affected by AD. Understanding the mechanisms by which nerve cells lose their ability to communicate with each other and the reasons for selective nerve cell death is at the heart of the worldwide scientific effort to discover the cause, or causes, of AD.

Epidemiology is an important research tool in determining risk factors and identifying potential interactions between genetic and non-genetic factors. Recent discoveries about the possible roles of inherited traits and education as risk factors for AD have taken researchers in new directions in their search for answers. In addition, researchers are looking for better ways to diagnose and treat AD, improve a patient's ability to function, and support the caregivers of people with AD.

The National Institute on Aging (NIA) has primary responsibility for research aimed at finding ways to prevent, treat, and cure AD. This report highlights recent progress in AD research conducted or supported by the NIA and other components of the National Institutes of Health (NIH), including the:

- ☐ National Institute of Diabetes and Digestive and Kidney Diseases
- ☐ National Institute of Neurological Disorders and Stroke
- ☐ National Institute of Arthritis and Musculoskeletal and Skin Diseases
- ☐ National Institute on Deafness and Other Communication Disorders
- ☐ National Institute of Mental Health
- ☐ National Center for Research Resources
- ☐ National Eye Institute
- ☐ National Institute of Allergy and Infectious Diseases

Additional AD research projects, which are not summarized in this report, are supported by the: National Cancer Institute; National Heart, Lung, and Blood Institute; National Institute of Dental Research;

National Institute of Child Health and Human Development; National Institute of Environmental Health Sciences; National Institute of Nursing Research; National Center for Human Genome Research; and Fogarty International Center.



Top of Document

Structure and Function of the Brain

The brain integrates, regulates, and controls functions for the whole body, governing cognition, personality, and the senses. We are able to speak, move, and remember because of complex chemical processes that take place in the brain. The brain also regulates body functions that occur without our knowledge or direction, such as our heart rate and breathing.

The human brain is made up of billions of nerve cells, called neurons, which communicate with one another through a large array of biological and chemical signals. Even more numerous are glial cells, which surround, support, and nourish neurons. Each neuron has a cell body, an axon, and dendrites. The nucleus within the cell body controls the cell's activities. The axon, which extends from the cell body, transmits messages to other neurons. Dendrites receive messages from axons of other nerve cells or from specialized sense organs.

Communications between neurons and other organs are transmitted through the synthesis and release of chemicals. When a nerve impulse reaches the end of the neuron, the signal triggers the release of neurotransmitters. These chemicals carry messages from the axons of nerve cells across the synapse (the gap between nerve cells) to the dendrites of other neurons. In this way, signals can travel back and forth across the brain in a fraction of a second. Millions of signals flash through the brain every moment.

Groups of neurons in the brain have certain jobs. For example, the cerebral cortex is a collection of neurons involved in thinking, learning, remembering, and planning.

Survival of nerve cells in the brain depends on the proper functioning of many interrelated systems that normally work in harmony. These systems control nerve cell activity related to communication, metabolism, and repair. The first system, communication between nerve cells, is described above. The loss or absence of any of several chemical messengers disrupts cell-to-cell communication and interferes with normal brain function.

The second system, metabolism, refers to the process whereby cells and molecules break down chemicals and nutrients into energy. Efficient metabolism in nerve cells depends on blood circulation to supply the cells with important nutrients, such as oxygen and glucose (a sugar). A sustained reduction in the supply of these nutrients can lead to nerve cell death.

The third system repairs and cleans up nerve cells. Unlike most other body cells, neurons live a long time. When neurons die, they cannot grow back or be replaced. Instead, living neurons constantly remodel themselves. Any disruption in cell cleanup and repair can have disastrous consequences for cell functioning. Research shows that the damage seen in AD is associated with changes in all three systems: nerve cell communication, metabolism, and repair.

[Top of Document](#)

Changes in the Brain in Alzheimer's Disease

In AD, the intricate process of communication between nerve cells breaks down. The destructive forces involved in AD ultimately cause nerve cell dysfunction, loss of connections between nerve cells, and death of some nerve cells. Death of neurons in key parts of the AD brain severely affects memory, cognition, and behavior.

AD destroys neurons in parts of the brain involved with cognition, especially the hippocampus (a structure deep in the brain that plays an important role in memory encoding). As the hippocampal nerve cells degenerate, short-term memory falters, and often, the ability to perform familiar tasks begins to decline as well. AD also attacks the cerebral cortex (the outer layer of the brain). The greatest damage occurs in areas of the cerebral cortex responsible for functions such as language and reasoning. Here, AD begins to take away language and change a person's judgment. Emotional outbursts and disturbing behaviors, such as wandering and agitation, appear with increasing frequency as the disease progresses.

In the final stages, AD wipes out the affected person's ability to recognize close family members or communicate in any way; the person becomes totally dependent on others for care. People with AD often live for years, ultimately succumbing to a number of other diseases, but most often pneumonia.

Two abnormal structures are found in the AD brain: amyloid plaques and neurofibrillary tangles. Located outside and around neurons, plaques contain dense deposits of an amyloid protein and other associated proteins. Neurofibrillary tangles are twisted fibers inside neurons. Progress has been made in determining the makeup of amyloid plaques and neurofibrillary tangles and in proposing mechanisms that could account for their buildup in AD.

Amyloid Plaques

In AD, plaques develop in areas of the brain related to memory. These plaques consist of beta-amyloid mixed with dendritic debris from surrounding cells. Beta-amyloid is a protein fragment clipped from a larger protein (amyloid precursor protein) during metabolism. However, researchers do not know whether amyloid plaques cause AD or result from it.

Amyloid precursor protein (APP) is a member of a larger gene family of membrane proteins. During metabolism, APP pokes through the nerve cell membrane (wall), part inside the cell, part outside. Pausing there only briefly, it is replaced by new APP molecules being produced in the cell. While APP is embedded in the membrane, enzymes called proteases split APP in two. Only when the splitting occurs at a particular spot on APP is beta-amyloid the substance that is set free.

After the splitting, how the beta-amyloid segment moves through or around the nerve cells is less clear. However, in the final stages of its journey, it is known to join up with other beta-amyloid filaments and fragments of dead and dying dendrites. Together, these form the dense and insoluble plaques that characterize AD.

Large numbers of beta-amyloid deposits in the brain can occur in older humans and some other mammals

without surrounding nerve cell changes. This finding suggests that beta-amyloid initiates and/or is only an early disordered product in a slow, multi-step process that ultimately leads to brain cell malfunction.

Several studies have centered on how beta-amyloid is processed and how APP is broken down by enzymes. Other investigations are seeking clues in beta-amyloid's environment. For example, substances near beta-amyloid may bind to it normally and thus keep it in solution. But in AD, according to one theory, something causes the beta-amyloid to drop out of solution and form insoluble plaques. Another candidate for the role of keeping beta-amyloid in solution is a form of a protein called apolipoprotein E (ApoE).

Other areas of research center on how beta-amyloid affects neurons. In one laboratory study, hippocampal neurons died when beta-amyloid was added to the cell culture, suggesting that the protein is toxic to neurons. Results of another recent study suggest that beta-amyloid breaks into fragments, releasing free radicals that attack neurons. Free radicals are unstable molecules that can do damage in the body. In AD, a buildup of oxygen free radicals, leading to the breakdown of nerve cell membranes, is thought to play a role in cell death.

The precise mechanism by which beta-amyloid may cause nerve cell death is a mystery. However, one recent finding suggests that beta-amyloid forms small channels in neuron membranes. These channels may allow excess amounts of calcium to enter the nerve cell, which is a lethal event.

Other recent studies indicate that beta-amyloid disrupts potassium channels, which also could affect calcium levels. Yet another study links beta-amyloid to reduced choline levels in nerve cells. Since choline is an essential component of acetylcholine, a neurotransmitter, this finding suggests a link between beta-amyloid and acetylcholine.

Beta-amyloid is not the only protein implicated in AD. Not long after the discovery of beta-amyloid, scientists found the protein that is the principal component of neurofibrillary tangles, the other hallmark of AD.

Neurofibrillary Tangles

Neurofibrillary tangles are abnormal collections of twisted threads found inside nerve cell bodies. They are the remains of the neuron's microtubules, the cell's internal support structures. The chief component of tangles is a protein called A68, a form of *tau*.

In healthy neurons, microtubules are formed like train tracks, long parallel rails with crosspieces, that guide nutrients from the bodies of the cells down the ends of the axons. In cells affected by AD, these structures collapse. *Tau* normally forms the crosspieces of the microtubules, but in AD it twists into paired helical filaments, two threads wound around each other. These paired helical filaments are the major component of neurofibrillary tangles. No one has discovered yet why the microtubules collapse, but according to one theory, it may be due to the presence of a gene product called ApoE4.

The collapse of nerve cell supports may result in the breakdown of communication between nerve cells and finally cause neurons to die. Still unknown, however, is whether abnormal processing causes *tau* to come away from the nerve cell supports or whether abnormal processing is the result of *tau* being gathered into the paired helical filaments. In addition, abnormal *tau* processing may simply indicate problems with metabolism of other, as yet unknown, nerve cell proteins. Sustained triggering of a single enzyme may disrupt other normal body functions that affect the survival of brain cells. To determine why

some nerve cells are vulnerable to AD and others are not, researchers first must understand the causes of abnormal processing and the regulation of certain enzymes.

Scientists may be able to develop animal models using mice that produce excess enzymes involved in *tau* processing. Further clues may lie in recent research using "knockout" mice (mice in which the regulation of an enzyme that helps process *tau* is altered). These and other routes could lead to an animal model for use in testing drugs to reverse or limit early brain cell damage caused by AD.



Top of Document

Advances in Identifying Risk Factors for Alzheimer's Disease

Although healthy aging does not result in dementia or AD, aging remains the most strongly associated risk factor for AD. Family history is another important risk factor. A history of AD in a parent or sibling increases the odds of developing AD by three to four times. Researchers believe that genetic (inherited) factors may be involved in more than half of the cases of AD. In addition, a severe head injury that leads to a brief loss of consciousness doubles the risk of developing AD later in life. These three risk factors--age, family history, and head injury--meet the accepted epidemiologic criteria for causal factors: they provide a plausible biological explanation, and their effects are strong and consistent.

Other risk factors that do not meet the above criteria have been studied, including exposure to environmental toxins (such as aluminum) or to chemicals (such as benzene and toluene). The detection of aluminum, zinc, and other metals in the brain tissue of people with AD is being studied to see whether such deposits influence the disease process or whether they are the results of disrupted brain structures. In addition, gender may play a role in the disease. Further research is needed to confirm recent data showing higher rates of AD among women. This finding may only reflect the effects of age, since women live longer, on average, than men.

It is becoming clear that the cause of AD is not a single factor, but a host of factors that interact differently in different people. In most cases, genetic factors alone are not enough to bring on AD. Genetic indicators have been found in some patients with the disease and in their relatives who do not yet show signs of impairment. Other risk factors may combine with a person's genetic makeup to increase the chances of developing AD.

Researchers studying the incidence and prevalence of AD and related dementias in later life seek to identify specific risk factors for AD and to show how and why AD develops. Incidence refers to the rate at which new cases of a disease occur. Prevalence is the percentage of the entire population with the disease at a given time. By studying people in different ethnic, racial, and social groups, scientists may discover additional risk factors for AD. These risk factors, in turn, may suggest new theories that can be tested regarding the disease's origin.

In the past year, researchers have examined risk factors that may speed up or slow down the onset of AD and increase or decrease a person's risk of AD. They focused on determining whether ApoE, education and occupation levels, a gene on chromosome 14, or zinc, aluminum, and other metals are related to AD. Their findings eventually may lead to treatment and prevention strategies.

The Link Between Alzheimer's Disease and ApoE

A gene is the biologic unit of heredity that has a precise location on a chromosome. Chromosomes are structures in the nucleus of cells that transmit hereditary information using a molecule called deoxyribonucleic acid (DNA). Genes direct the manufacture of every enzyme, hormone, growth factor, and other protein in the body. They help determine a person's traits, for example, what he or she looks like. Genes are made up of four chemicals, or bases, arranged in various patterns within the DNA. Each gene has a different sequence of bases, and each one directs the manufacture of a different protein. Even slight alterations in the DNA code of a gene can produce a faulty protein. And a faulty protein can lead to cell malfunction and eventually disease.

Genetic research has turned up evidence of three gene alterations that are more common in AD patients than in the general population. One, the ApoE4 gene on chromosome 19, has been linked to the most common form of AD, called late-onset AD, which appears in older people. Researchers also have found genes on chromosomes 14 and 21 that are more common among people who develop AD earlier, in middle age.

Everyone has ApoE, which helps transport cholesterol in the blood throughout the body. The gene for ApoE occurs in three versions: ApoE2, ApoE3, and ApoE4. Every person inherits two ApoE genes, one from each parent. Scientists are studying people with different versions of this gene. ApoE3 is the most common one found in the general population. However, ApoE4 occurs in about two-thirds of all late-onset AD patients and is not limited to people with a family history of AD.

Collaborating researchers at the Duke University General Clinical Research Center and the Joseph and Kathleen Bryan Alzheimer's Disease Research Center in Durham, North Carolina, studied the relationship between ApoE4 and AD. Their research was supported by the NIA and the National Center for Research Resources (NCRR). These scientists found that the risk for AD in people with the gene for ApoE4 is three times greater than that for other people. For example, a 78-year-old person with two copies of the gene for ApoE4 has a 98 percent chance of having the disease, with one copy a 60 percent chance, and with no copies a 25 percent chance.

In addition, this research shows that the presence of ApoE4 also lowers the age of onset of AD. On average, people with two copies of the gene for ApoE4 start showing AD symptoms before age 70 and are eight times more likely to develop AD than those who have two copies of the more common ApoE3 version. For those with no copies of ApoE4, the average age of onset is older than 85 years. According to these scientists, AD risk increased because the age of onset decreased. In some unknown way, ApoE4 may speed up the AD process.

These researchers also found that ApoE is localized in the senile plaques and neurofibrillary tangles found in AD. Moreover, Duke University researchers now believe that ApoE is located in all neurons in both healthy and AD brains.

Researchers at the Mayo Clinic in Rochester, Minnesota, followed 71 older patients with mild memory impairment. Almost half had clinical dementia after 3 years. Over two-thirds of those with clinical dementia with a copy of the gene for ApoE4 continued to decline, and ApoE4 best predicted who would decline. ApoE4 appears to mark susceptibility to AD. However, the presence of ApoE4 in a blood sample does not predict AD. A person can have ApoE4 and not get the disease, and a person can get AD without having ApoE4.

The relatively rare protein ApoE2 may protect people against the disease; it seems to lower the risk for AD and increase the age of onset. For instance, people with one ApoE2 gene and one ApoE3 gene have only one-fourth the risk of developing AD as people with two ApoE3 genes.

Some researchers supported by the NIA and NCRR exploring the function of the protein product of ApoE4 point to beta-amyloid. While the ApoE4 protein binds rapidly and tightly to beta-amyloid, the ApoE3 protein does not. Normally, beta-amyloid is soluble, but when the ApoE4 protein latches on to it, the amyloid becomes insoluble. This may mean that it is more likely to be deposited in plaques. Studies of brain tissue suggest that ApoE4 increases deposits of beta-amyloid and that it directly regulates APP.

Other researchers believe that the presence of ApoE in neurons may affect certain cell processes and how synapses function. Also, scientists conducting test tube studies found marked differences in the rates at which ApoE3 and ApoE4 bind to *tau* protein and to a similar protein found in dendrites. One hypothesis suggests that the ApoE4 product allows the microtubule structure to come undone in some way, leading to the neurofibrillary tangles.

While still controversial and far from proven, the hypotheses surrounding ApoE4 are driving new research. One next step is to see how *tau* and beta-amyloid react with ApoE in its several forms in living cells. Other experiments will be designed to determine the actions and role of ApoE. Once these are clear, it should be easier to understand how ApoE's function might be affected by drugs. For instance, if ApoE2 turns out to be beneficial, then substances that mimic its effects might be developed to help slow or prevent the progress of AD.

Theories surrounding ApoE4 are not confined to the proteins. Its effect on dendrites intrigues some scientists, because of findings that dendrites in patients with the ApoE4 gene are shorter, pruned back apparently by some unknown agent. The result may be that, compared to normal dendrites, these pruned dendrites cannot form as many connections with other nerve cells. Although this pruning also can occur in people without the ApoE4 gene, it happens 20 to 30 years earlier in people with ApoE4.

In addition, environmental factors may interact with genetic factors. Researchers at the Neurological Institute in New York City believe that repeated head injuries do not increase the risk of developing AD without ApoE4. However, when ApoE4 is present, these scientists found that repeated head injuries increase risk for AD by 10 times.

With ApoE, scientists have a biological indicator for AD for the first time. ApoE can be used to sort populations and follow the subgroups with the hope of finding other risk factors. Scientists still must learn how ApoE and its various genes function in the brain and relate to other risk factors for AD. Larger population-based studies are needed to clarify the link between ApoE4 and AD, and to confirm the protective effect of ApoE2. Further explanation of preliminary findings may lead to ways to reduce the effects of ApoE4, develop drugs to treat or prevent AD, and ultimately, decrease the occurrence of AD. Moreover, some scientists suggest that testing for the ApoE4 gene someday may help in the diagnosis of AD.

Genes in Early-Onset Alzheimer's Disease

AD can strike early and often in some families--often enough to be singled out as a separate form of the disease, called early-onset familial AD (FAD). Combing through the DNA of some of these early-onset FAD families, researchers at St. Mary's Hospital Medical School in London, England, previously have found an abnormality in one gene on chromosome 21 that is common to a few of the families. And they

have mapped another gene, which occurs in a much larger portion of early-onset families, to a region on chromosome 14.

The gene on chromosome 21 carries the code for an abnormal form of APP, the parent protein for beta-amyloid. The discovery of this gene supports the theory that beta-amyloid plays a central role in some forms of AD, although it has been found only in about 5 percent of early-onset FAD families. In addition, the gene on chromosome 21 is the gene involved in Down syndrome. Down syndrome is similar to AD in one respect. People with Down syndrome have an extra version of chromosome 21, and, as they grow older, usually develop plaques and tangles like those found in AD.

Compared to the chromosome 21 gene, the gene on chromosome 14 occurs more often in people with FAD. However, so far, no one knows exactly what gene it is. The gene has been tracked to a specific region on chromosome 14. Scientists at the University of Washington at Seattle still are trying to find the gene among the 10,000 or so DNA bases in this region.

Lower Educational and Occupational Levels Associated With Alzheimer's Disease

Scientists at Columbia University in New York City have established a relationship between increased risk for AD and lower educational and occupational levels. The researchers found that people with either lower educational or occupational levels have at least twice the risk for developing AD, compared to those who have had 6 to 8 or more years of schooling. The risk is three times greater when low occupation and low education occur together.

For 4 years, researchers administered yearly neuropsychologic tests to 593 people age 60 and older to see if any of them began to show signs of dementia. The results were analyzed based on educational level (kindergarten through college) and occupational level. A low level of education was set at 8 years of schooling, and occupational levels were based on U.S. Census categories. At the study's end, over 25 percent of the participants showed some sign of dementia.

These researchers do not know why low occupation and education are linked with AD. They believe that higher occupational and educational backgrounds may allow people to cope better with the effects of AD for a longer time before symptoms occur. People with more education may develop a protective reserve of brain cells or synapses. Also, increased mental capacity may allow these people to find additional ways to do daily activities. Or, education may be related to another factor, such as socioeconomic or nutritional status, which may be the reason for increased risk.

This study adds information about psychosocial factors related to AD. Investigators and caregivers now have another factor to consider when evaluating whether failing memory and confusion are signs of AD or some other, possibly treatable, problem. If some aspects of life experience can delay the onset of AD for even a short time, the overall prevalence and costs of the disease will be reduced significantly. This also could enhance the quality of life for many people.

Environmental Suspects

Certain environmental factors, such as metals and poisons carried in foods, may play a role in the development of AD. The most studied of these factors are aluminum and zinc. Researchers continue to study whether some metals are related to the development of disease markers such as plaques and tangles in brain tissue of AD patients. To date, no conclusive evidence links metals such as aluminum or zinc to AD.

One of the most publicized and controversial hypotheses in AD research concerns aluminum. This aluminum theory goes back to the 1970's, when researchers found traces of aluminum in the brains of AD patients. Many studies since then either have not been able to confirm this finding or have produced questionable results.

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

Other studies have shown that groups of people exposed to unusually high levels of aluminum have no increased risk of AD. Moreover, aluminum in cooking utensils does not get into food, and the aluminum that does occur naturally in some foods, such as potatoes, is not absorbed well by the body. On the whole, most scientists now believe that there is little chance that exposure to aluminum causes AD.

Zinc has been implicated in AD in two ways, some reports suggesting that too little zinc is a problem, others that too much zinc is at fault. Too little zinc was suggested by autopsies that found low levels of zinc in the brains of AD patients, especially in the hippocampus. There is some evidence that zinc deficiency can add to the symptoms of AD.

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



[Top of Document](#)

Advances in Diagnosing Alzheimer's Disease

A definitive diagnosis of AD is based on the presence of plaques and tangles in the brain. Plaques and tangles can be found only by examining brain tissue (a brain biopsy), and this procedure usually is done only as part of an autopsy.

Currently, no definitive test exists to diagnose AD. However, a probable diagnosis of AD can be made based on the patient's medical history, a physical examination, and tests of mental ability. Several other conditions, some of which are treatable, also may cause memory or other cognitive deficits and must be ruled out. These include thyroid gland problems, drug reactions, depression, brain tumors, and dementia caused by blood vessel disease in the brain.

A patient history includes a review of present and past medical problems, as well as an examination of current ability to carry out daily activities. Clinical analyses used to decide whether a person has AD or another disease include tests of blood and urine samples and an examination of a small sample of cerebrospinal fluid.

Neuropsychological tests are used to evaluate a person's mental abilities in many areas, including

memory, problem solving, attention, calculation, and language. Brain imaging also may be used to detect abnormalities in the brain. The results of all tests and the patient's medical history help the doctor determine if symptoms are caused by AD or by another condition.

Early and accurate diagnosis of AD has a major effect on the progress of research on dementia and is of utmost concern to patients and their families. Although the early and accurate diagnosis of AD is difficult, a reliable diagnosis with 80 to 90 percent accuracy (when compared to autopsy findings) can be obtained in many specialized centers.

Improving the diagnosis of AD using various procedures would allow patients and their families to know what stage of the illness they are dealing with and help them plan for the future. It also would improve the planning and design of drug trials, because drugs may work more effectively to alter the course of the disease in patients with early-stage AD. These methods would help identify patients early in the course of the illness when they have experienced the smallest degree of nerve cell damage and cognitive loss. The earlier and more accurate the diagnosis, the greater the gain in managing the clinical course of the illness, determining its natural history, and providing information about its causes and treatment.

The NIA supports research to identify dementia indicators; develop tests and methods related to differential diagnosis, screening, etiology (the study of the causes of the disease), risk factors, and family history; improve research designs; and refine diagnostic criteria.

One goal of current research is to develop an accurate test for AD. The search continues for a biological indicator that can identify AD cases very early in the course of the disease, when treatment still could be effective. Neuropsychologic tests are needed that pinpoint the stages of AD. These tests would separate people who are in the earliest stages of AD from people who have cognitive deficits that are related to healthy aging. Brief cognitive screening tools are proliferating. However, the relationship of the results of one test to another, to careful clinical diagnosis of abnormalities, and ultimately to brain cell death remains unknown.

Experimental technology for imaging the brain continues to develop rapidly. New procedures include positron emission tomography (PET), single photon emission computed tomography (SPECT), magnetic resonance imaging (MRI), and magnetic resonance spectroscopy imaging (MRSI). MRI provides high-resolution images of the brain. MRSI allows observation of various metabolites in the brain without the use of radioactive tracers. Metabolites are substances that are produced when energy is made available for cell use. Scientists are working to learn how metabolites change with aging and with AD and how to relate these changes to cognitive impairment. MRSI may offer a way to establish early diagnosis, determine prognosis, monitor patients, and evaluate treatment efficacy.

Researchers have yet to understand the relationship between the results of various brain imaging methods and the person's clinical condition. In addition, methods used to analyze imaging results need to be standardized. In the future, researchers hope to put information from imaging techniques that evaluate structure and those that analyze function together into a unified diagnostic summary.

Research on an Eye Test To Diagnose Alzheimer's Disease

Researchers at the Harvard Medical School in Boston, Massachusetts, are working on developing a simple eye test for detecting the presence of AD. Eventually this test may help diagnose patients with AD. Preliminary results suggest that monitoring pupil dilation (expansion) after exposure to certain eye drops may one day be the basis of an easy, accurate way to diagnose AD.

Data in this study suggest that the pupils of healthy people or those with non-AD dementia dilated about 5 percent after receiving the eye drops. The pupils of people with AD dilated 23 percent. This test pointed to AD in 18 of 19 people believed to have AD. Furthermore, pupils seemed to be sensitive to the chemical very early in the course of the disease, when emerging treatments are likely to be most effective. This test now must be studied in many more people to determine whether it holds up in different types of people with different types of AD, and distinguishes AD from other neurologic illnesses.

Changes in Immediate Visual Memory Predict Cognitive Impairment

NIA researchers have found that changes occurring over 6 years in immediate visual memory performance, assessed by the Benton Visual Retention Test (BVRT), predict AD before the onset of cognitive symptoms. Immediate visual memory refers to the ability to remember and name, within seconds, things seen. The BVRT requires subjects to reproduce geometric designs from memory after studying them for 10 seconds. Each test consists of 10 separate designs with 1 or more figures, and the score is the total number of errors made in reproducing the designs.

Researchers in the NIA's Baltimore Longitudinal Study of Aging examined data for 254 men and 117 women, who were administered cognitive, neuropsychologic, and neurologic tests between 1986 and 1992. These people were generally healthy and ranged in age from 55 to 95 at the initial testing. Six of them had probable AD, and one had definite AD.

Compared to those without AD, subjects with the disease had larger changes in the numbers of errors in immediate memory performance over the 6 years prior to the onset of AD. This finding implies that AD may be identified by changes in memory performance sooner than other changes can be detected by clinical evaluation. Six-year change in immediate visual memory performance also predicted cognitive performance from 6 to 15 years and from 16 to 22 years later. This was true even after adjusting for the influences of age, general ability, and initial immediate memory.

In addition, these results suggest that change in recent memory performance, a critical component in diagnosing AD, may be an important precursor of the development of the disease. Recent memory performance generally refers to recall after a short delay, such as 20 minutes.

The results show the value of longitudinal studies because predictions of risk for subsequent disease are possible only when baseline and followup data are gathered before the onset of disease. This is particularly important for AD, because little is known about the earliest stages of AD. However, this period is likely to be when the disease is most responsive to treatment.



[Top of Document](#)

Advances in Treating and Preventing Alzheimer's Disease

There currently is no effective way to treat or prevent AD. However, several substances are being tested to see if they can slow or reverse the decline in those behavioral and cognitive skills that are impaired by AD. Pharmacologic and behavioral treatments for the non-cognitive behavioral symptoms related to AD also are being studied. These symptoms include aggression, agitation, wandering, depression, sleep

disturbances, and delusions.

The drug tacrine (also known as THA or Cognex) may temporarily slow the rate of decline in memory and thinking ability in some patients who are in the mild and moderate stages of the disease. Experimental drug treatments may be available to AD patients through clinical trials conducted at large teaching hospitals and universities. Several of these experimental drugs have shown promise in easing symptoms in some patients.

Moreover, medications may help control behavioral symptoms, thereby making some patients more comfortable and making their care easier for caregivers. For example, several drugs now in use may improve sleep patterns, reduce agitation and wandering, or ease anxiety and depression.

Scientists studying drug and non-drug treatments seek to reduce disruptive behaviors, allow patients to live in the least restrictive manner possible while maximizing their dignity and independence, reduce caregiver stress, and keep or re-establish patients' self-care abilities. In addition, effective treatments would decrease significantly the economic costs to families and society by reducing the need to institutionalize patients. Overall, these research efforts are designed to increase the intellectual, emotional, and social well-being of patients, families, and caregivers.

In 1994, the NIA funded a 5-year study to screen for potential toxic effects of new drugs to treat AD. The data gathered will be used to file Investigational New Drug requests with the Food and Drug Administration so that compounds can be taken quickly from animal testing into human clinical trials.

Thirty-five sites in the Alzheimer's Disease Cooperative Study Unit (ADCSU) are located primarily at the Alzheimer's Disease Research Centers and Alzheimer's Disease Core Centers. The ADCSU is conducting trials of deprenyl and vitamin E, drugs used to treat agitation, an anti-inflammatory agent, and estrogen. In addition, the ADCSU is testing neuropsychologic instruments in the areas of cognitive change, behavioral change, global assessment, and activities of daily living. The ADCSU also is adapting instruments for use with people who are severely impaired and with those who do not speak English. Future ADCSU work will involve designing trials to evaluate whether a substance can prevent AD.

In addition, postmenopausal estrogen replacement therapy, long-term use of anti-inflammatory drugs, and cigarette smoking have been implicated as having a protective effect against AD. These all need to be confirmed by further and more careful studies.

Inverse Association of Anti-Inflammatory Drugs and Alzheimer's Disease

Anti-inflammatory drugs are used to ease symptoms of arthritis or related conditions. Recently, they have been proposed as a means of slowing the progression of AD symptoms. Studies of twins suggest that the use of anti-inflammatory agents may relate to the etiology and prevention of AD.

NIA-funded researchers at the Duke University Medical Center and Johns Hopkins University School of Hygiene and Public Health studied 50 sets of older twins with AD. They found a lower incidence of AD among those who had used anti-inflammatory drugs to treat arthritis. These findings suggest that inflammatory mechanisms may be involved in the development of AD. They also indicate that anti-inflammatory agents may prevent or delay the onset of AD symptoms.

Estrogen

Preliminary data from previous animal and human studies suggest that estrogen may protect older women against AD. However, recent research has generated some conflicting results. Initial results from one study by researchers at the University of Washington, Seattle, provide no evidence that post-menopausal estrogen replacement therapy influenced the risk of AD in women. Using computerized pharmacy data, these researchers compared the use of estrogen replacement therapy by 107 women with AD and 120 women without AD. Estrogen use was not associated with AD.

Other NIA-funded researchers at the University of Southern California School of Medicine, Los Angeles, analyzed data for 138 older women who had died and whose death certificates listed AD or related dementias. Their results suggest that risk of AD and related dementia was lower in estrogen users than in non-users. Risk of AD decreased significantly with increasing estrogen dose and with increasing duration of estrogen use. Risk of AD also was associated with variables related to estrogen levels produced naturally in women. Data also suggest that risk of AD increased with increasing age at the onset of menstruation and decreased with increasing weight.

Overall, this study suggests that the increased incidence of AD in older women who have undergone menopause may be due to estrogen deficiency. Further research is needed to determine whether estrogen replacement therapy can slow down AD-related nerve cell death, and delay the onset of AD or prevent it altogether. Additional research will allow scientists to analyze how and why these and other studies have conflicting results.

Research on Dementia Special Care Units

Another line of AD research sponsored by the NIA concerns the effectiveness of special care units (SCU's) across the Nation. The results of these studies may provide ways to improve care for patients with AD and related dementias.

Dementia SCU's are long-term care settings designed to meet the needs of people with AD and related mental impairments. SCU's emerged in the 1980's as a care option for patients with AD. Forces creating a demand for specialized care include the growing numbers of older people; the recognition that the care needs of people with dementia differ from those of physically frail people; and the widespread concern that standard nursing home care has been unresponsive to the special needs of people with AD and related disorders, their families, and caregivers.

Since their beginnings, SCU's have proliferated rapidly and grown in diversity. The 1990-91 National Survey of Special Care Units in Nursing Homes found that of the Nation's 15,555 licensed nursing homes, 9.6 percent (1,497 nursing homes) had SCU's, with an estimated capacity of about 47,878 residents. While most nursing homes with SCU's presented some features considered important for SCU's, only 647 met all of them. Projections from this survey suggest that 16.7 percent of all nursing homes will offer SCU's in 1995.

To explore the effectiveness of SCU's, the NIA funded a 5-year multi-center Special Care Unit Initiative, beginning in 1991. Under this program, the NIA financed 10 research projects to examine SCU's throughout the United States.

Several research issues have emerged since 1991. There is a lack of standardization about what constitutes an SCU versus a non-SCU. Use of uniform descriptive data is critical because SCU's vary in size, age of patients, and whether or not patients are segregated from the general nursing home population. SCU's also can differ in how they recruit residents for participation in studies. Research

studies need to establish the diagnosis and cognitive level of residents to identify a sample group for study.

The proliferation of SCU's means that for the first time in the United States, administrators and staff members in numerous nursing homes are developing methods of care specifically for their residents with dementia. Better methods of care cannot be realized without formal research to describe, compare, and evaluate the various methods being used. There still is a need for more research on classification, design characteristics, costs, and effectiveness of SCU's. For public policy purposes, the most important research questions pertain to the effectiveness of SCU's for their residents, the residents' families, and the unit staff members; and the impact of SCU's on residents with and without dementia in non-specialized nursing home units.

Further research will provide a better idea of what constitutes "special care" and identify which features of SCU's are most important in terms of environment, staffing, activities, care planning, admission policies, size, and patient segregation. Additional studies will determine whether effective SCU's cost more than traditional nursing home units. Eventually, the results of these studies will enable caregivers and health care insurers to compare options when shopping for long-term care facilities.

Alzheimer's Disease Centers Program

The NIA funds 28 Alzheimer's Disease Centers (ADC's) at major medical institutions across the Nation. The centers conduct a wide range of research, including studies on the causes of AD and investigations aimed at diagnosing, treating, and managing the symptoms of the disease. The ADC Program promotes research, training and education, technology sharing, and multi-center and cooperative studies of diagnosis and treatment. Each ADC has administrative, clinical, neuropathology, and education and information-sharing cores, or sections. Some ADC's include additional cores, such as neuroimaging and data analysis.

Fifteen comprehensive ADC's have fully-funded basic, clinical, and behavioral research projects. Areas of study range from the basic mechanisms of AD to managing the symptoms and helping families cope with the effects of the disease. The other 13 ADC's are Alzheimer's Disease Core Centers, which provide resources to AD researchers.

A program was initiated in 1990 to add satellite clinics linked to the ADC's. Currently, 27 satellite clinics at 21 ADC's offer diagnostic and treatment services and collect research data in underserved, rural, and minority communities. These programs allow members of culturally and ethnically diverse communities to take part in research and clinical drug trials associated with parent ADC's.

Much of the success of AD research in this country during the last 10 years can be attributed to resources provided at the ADC's, including the recent discovery of the importance of chromosome 14 in FAD and the identification of inherited risk factors related to ApoE. The ADC's enhance AD research by providing a network for sharing new ideas as well as research results.

Other initiatives funded by the NIA depend on the ADC's, including regular research grants, the Consortium to Establish a Registry for Alzheimer's Disease, and the ADCSU. The ADC's provide resources for these efforts, such as patient data, brain and other tissue samples, and molecular probes.



Top of Document

Research Conducted by Other NIH Institutes

National Institute of Diabetes and Digestive and Kidney Diseases

National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) research that relates to AD generally falls within two areas. The first focuses on mechanisms involved in abnormal metabolic processes. The second concerns the molecular and biochemical mechanisms of cells, including the roles of neurotransmitters and ion channels.

This year, NIDDK grantees reported progress in understanding the metabolic processes leading to the formation of abnormal amyloid protein, a major component of plaques in the brain. Although the ultimate cause of neuronal cell death remains undetermined, some evidence suggests that the buildup of abnormal amyloid protein may be involved in this process.

One goal of NIDDK-supported research is to understand the biochemical mechanisms underlying amyloid diseases. Researchers are learning how APP, a normally soluble protein, is transformed into the insoluble fibers that build up in AD plaques. This work focuses on a form of abnormal amyloid protein that has been implicated in amyloid polyneuropathy, a neurologic disease. This form of abnormal amyloid protein is similar but not identical to the form found in AD. These researchers identified a gene mutation that alters an intermediate step in the formation of amyloid and appears to be related to abnormal amyloid protein production. The findings suggest that certain gene mutations may have metabolic effects that determine the development of amyloid disease.

National Institute of Neurological Disorders and Stroke

The National Institute of Neurological Disorders and Stroke (NINDS) is the principal source of support for neurological research in the United States and a major participant in the study of AD. Basic studies are aimed at determining the underlying causes of AD with the ultimate goal of prevention. Clinical research seeks to improve the diagnosis and treatment of patients.

Scientists at the NINDS and NIA have discovered that adding beta-amyloid to normal skin cells causes them to undergo the same type of failure at the molecular level previously shown in skin cells of patients with AD. By placing a solution with low levels of beta-amyloid in culture with normal human skin cells, the scientists produced changes in potassium channel function similar to those seen in skin cells from AD patients. Beta-amyloid is the main component of plaques found in brain tissue in AD. This finding suggests that beta-amyloid may cause the abnormal process that leads to memory loss even before it congeals into plaques. This research may lead to alternative explanations of the causes of memory loss, one of the earliest and most common symptoms of the disease.

Last year, researchers in the same laboratory showed that skin cells from people with AD have defects that interfere with the cell's ability to regulate its concentrations of potassium and calcium ions. The flow of potassium and consequent uptake of calcium are especially critical in brain cells responsible for memory formation and information storage.

Recently, after treating one group of the skin cells with soluble beta-amyloid for 48 hours, scientists found that a specific potassium channel was absent in all but one of the cells. However, a functional potassium channel was present in 94 percent of untreated cells. Results of further testing suggest that

beta-amyloid selectively targets this specific potassium channel, which had been absent in skin cells of AD patients.

These researchers now are working to see if similar potassium channel dysfunction occurs in central nervous system neurons. The scientists have discovered similar defects in nerve cells of the olfactory system (related to the sense of smell), suggesting that such defects may be present in brain cells.

National Institute of Arthritis and Musculoskeletal and Skin Diseases

Researchers at the National Institute of Arthritis and Musculoskeletal and Skin Diseases have made strides in finding a treatment for amyloidosis (a buildup of amyloid protein in various body tissues). This research may lead to a possible treatment for AD, because a major feature of AD is brain deposits of amyloid or amyloid-like material.

Some forms of amyloidosis are inherited. One of these forms, familial amyloid polyneuropathy (FAP), is caused by a mutation of the transthyretin (TTR) protein. Scientists have developed a method for separating normal and mutant TTR in bodily fluids, allowing rapid screening and diagnosis. This method also allows the ratio of normal to mutant TTR to be measured over time.

These researchers also have reported on liver transplants in patients with FAP. Almost all normal and abnormal TTR is produced in the liver. Patients undergoing liver transplants for advanced disease showed important improvements in their conditions. The amount of mutant TTR present after the transplant was reduced markedly. After surgery, patients had only normal TTR. This is the first successful therapy in patients with FAP.

National Institute on Deafness and Other Communication Disorders

The National Institute on Deafness and Other Communication Disorders (NIDCD) studies the normal and disordered processes of balance, smell, taste, voice, speech, hearing, and language. The NIDCD's chemosensory (smell and taste) research program includes studies of the olfactory receptor cell (a nerve cell in the part of the nose that senses smell). Normally, these nerve cells are replaced continually in the body. An important aspect of this research is the potential for developing new strategies to treat nerve cell loss caused by aging, injury, and diseases, such as AD.

Scientists supported by the NIDCD recently examined the development of human olfactory neurons transplanted into the brains of animals. They studied the interaction of these transplanted neurons with other brain cells. The transplanted neurons not only survived, but developed and grew nerve fibers that entered and mingled with the animal's other nerve cells. The fact that donor olfactory neurons developed and integrated with other nerve cells means that the possibility exists of forming new neuronal connections.

The capacity of transplanted olfactory neurons to produce new nerve cells is of wide interest not only with respect to chemosensory function, but also as a model for studying neuron replacement. Further research on transplanted neurons may show that biological repair of nerve damage from neurodegenerative diseases, including AD, is possible.

National Institute of Mental Health

National Institute of Mental Health (NIMH) research on AD spans from the genetics and molecular

biology of the disease to the psychosocial stresses faced by family members.

The NIMH Diagnostic Centers for Psychiatric Linkage Studies of Alzheimer's Disease identify siblings with and without AD for ongoing studies. The centers' goal is to establish a national resource of cell lines and clinical data from people with AD and their key relatives.

Advances in the molecular genetic study of AD may show how the disorder develops and offer ways to identify those at risk for the purposes of early intervention. Neurofibrillary tangles found in the AD brain largely consist of abnormal forms of the cellular protein *tau*. In the normal brain, *tau* binds to microtubules that provide structural support for cells, including neurons. In AD, *tau* takes the form of twisted fibers and does not bind to microtubules.

Using techniques from molecular genetics, NIMH researchers have identified tissue at risk for AD and other neurodegenerative processes. They also have developed a new probe, an antibody that identifies and interacts exclusively with neurons that are vulnerable to the disease. Antibodies are immune system molecules. Antigens stimulate the production of antibodies. Each antibody has a unique amino acid sequence that allows it to interact with only a certain antigen. The above antibody probe stains for a different antigen than expected. This finding suggests that a host of unknown pathologic indicators or gene products may occur in AD.

In test tube studies, NIMH scientists have been able to grow neuroblasts (immature nerve cells), which were taken from inside the noses of AD patients and healthy people. They have found that AD neuroblasts have increased levels of APP fragments. These fragments are thought to include the toxic protein beta-amyloid. The amount of fragments decreases when theophylline is added to the cells, suggesting toxicity and a potential therapeutic intervention.

Recent advances in basic neuroscience research link brain structures and functions involved in AD and help explain some AD symptoms. Using animal models, NIMH-supported researchers have found a connection between two areas of the brain, one of which allows people to forget an emotion-linked memory that no longer is useful. When this part of the brain is damaged, it may fail to erase an emotional memory or prevent an emotional response. This research may bear on AD patients' inappropriate emotional responses or inability to remember emotionally significant information.

NIMH researchers strive to reduce problematic symptoms of AD and help families care for these patients. They are studying the relationship between disturbed sleep, altered sleep-wake cycles, episodes of stopped breathing, daytime sleepiness, and sundowning (or nighttime confusion). By doing so, NIMH-funded researchers hope to decrease sleep problems and confusion and reduce some disability in AD patients. Preliminary studies of patients with dementia and normal breathing during sleep show they have less confusion in the morning or the same amount of confusion as during the previous night. This finding suggests that increased confusion related to a decrease in the amount of oxygen breathed in during sleep may represent an early phase of sundowning. Studies also are being done of the clinical efficacy of several medications commonly used for sundowning.

An NIMH-supported program for caregiving spouses of AD patients delayed nursing home placements up to 6 months. This program offered individual and family counseling and a caregiver support group. Compared to other caregivers not in the program, the supported spouses showed less decline in their own mental and physical health, and derived more satisfaction from their social support networks. Results suggest that psychosocial interventions may relieve some burdens of long-term caregiving for chronically impaired older adults. This relief may translate into major cost reductions for health care delivery systems.

These findings are important, given the high cost of nursing home care and the increasing number of people with AD.

NIMH-funded research indicates that caregiving stress negatively affects the caregiver's mental health (increased depression), immune system function, and physical health. These studies show that AD caregivers perform lower on measures of their bodies' ability to fight diseases and have more infectious disease episodes than do non-caregivers. Older, caregiving spouses' immune functions fail to return to the level found in controls over a sustained period. Caregivers also show a lower antibody buildup in response to influenza vaccination.

Male caregivers may be at risk for the cardiovascular effects of caregiving stresses. Higher levels of triglycerides ("bad" cholesterol) and lower levels of high-density lipoproteins ("good" cholesterol) have been found among male caregivers. Male caregivers also have higher levels of: anger, coronary-prone behavior, and use of avoidance when coping. These results provide the foundation for more targeted interventions with caregivers who can be identified as more or less at risk for mental health and physical health problems.

Although most older Americans lead healthy lives unaffected by significant mental disorder, up to 12 percent of people age 65 and older experience an anxiety disorder, depression, or some form of dementia. Mental disorders in late life are not an outcome of normal aging. Instead, they are illnesses that result in significant disability, dependency, and early death. Sleep problems can lead to inappropriate use of sleeping pills, fatigue, and disorientation, which in turn reduce quality of life and increase the chances of illness. Of the 5 percent of older Americans in nursing homes, up to one-fifth suffer from some form of unnecessary depression, which increases the risk of mortality.

Mental disorders in older people often occur along with physical illness and pain symptoms. Older people are less likely to seek mental health services, and many seek assistance from primary care physicians when faced with mental illness. Unfortunately, mental disorders in older people typically go undetected, and many do not receive available treatments. This is particularly tragic for depressed older people who commit suicide. More than 70 percent of older men (the highest risk group for suicide in this country) visit their primary care physicians within 1 month before committing suicide.

Safe and effective treatments are available for depression, anxiety, and sleep disorders. Efforts to refine treatments include studies of how people metabolize psychotropic medications (drugs that act on the mind) with and without other medications for physical disorders. Research on psychosocial treatments alone and in combination with medications over long periods are providing important data for recommended treatment practices. Like other diseases, it appears that many mental disorders require long-term treatments.

National Center for Research Resources

Through its national network of clinical, animal, and other research resource centers, the National Center for Research Resources (NCRR) supports studies to advance understanding and treatment of AD and other disorders affecting older Americans.

In addition to research at Duke University on ApoE, the NCRR supports several potential therapies for AD at Regional Primate Research Centers (RPRC's). Researchers at the University of Washington RPRC have used a compound (leupeptin) that accelerates brain aging in rats to stimulate an effect similar to AD in aged monkeys.

At the California RPRC, scientists found that age-related neuron weakening in part of the brain can be prevented by adding nerve growth factor (NGF) in primates. An NGF is a protein that fosters development of nerve cells and may protect certain nerve cells from damage. It supports cells that produce the vital neurotransmitter, acetylcholine. Other neurotrophic factors (components that help maintain body tissues and are regulated by nervous functions) also may be useful in therapy for this degeneration. Using gene therapy techniques, researchers have found that NGF-producing fibroblasts (cells that are part of the tissue that binds together and supports the various body structures) survive up to 6 months in the adult primate brain.

At the Wisconsin RPRC, scientists are mapping the distribution of neurotrophins and their receptors. This work will help identify growth factors that may allow rescue of neurons in brain regions affected by AD.

National Eye Institute

The National Eye Institute continues to support a study of human binocular vision and motion perception. Binocular vision is the merging of images from both eyes into a single image perceived by the visual cortex of the brain. Motion perception is the ability to perceive clearly the direction and speed of a moving object. This research focuses on interactions among the neurological mechanisms underlying these aspects of vision and stereopsis. Stereopsis is the ability to combine the images of two pictures of an object seen from slightly different viewpoints. It refers to how people see something as both a solid and three-dimensional object. These study areas may provide important clues about the perceptual consequences of neurologic dysfunctions in AD.

Specific areas under study are: the coexistence of stereopsis and binocular competition; the regions in the brain associated with binocular suppression (relative to the analysis of motion information) and visual attention; interactions between stereopsis and depth perception in specifying structure from motion; and motion perception and stereopsis in AD patients.

National Institute of Allergy and Infectious Diseases

Studies conducted by the National Institute of Allergy and Infectious Diseases (NIAID) with the greatest relevance to aging and AD involve research to develop a drug to prevent scrapie. Scrapie is an infectious, neurodegenerative disease of sheep and goats. Scrapie is similar to AD in that accumulations of abnormal protein form amyloid plaques in the brain. One advantage of scrapie research is that, unlike AD research, animal and cell culture models already exist in which to study amyloid formation and therapeutic strategies. Current NIAID research on scrapie offers potential for understanding the clinical development of AD.

The agent that causes scrapie is an unusual infectious particle that contains no nucleic acid and consists of a single protein, called PrP-res. NIAID scientists found that when a normal protein typically found in the brain (PrP-sen) interacts with an altered form of itself, the altered form is converted to PrP-res. When PrP-res builds up in the brain, amyloid plaques form. Although the major proteins forming plaques differ in scrapie and AD, an understanding of how amyloid is formed in scrapie may provide insights about plaque formation in the AD brain.

NIAID intramural scientists have found that Congo red, a chemical dye, can delay the onset of scrapie in mice by preventing the buildup of PrP-res in the brain infected with scrapie. The fact that Congo red shows some efficacy in preventing the development of scrapie in laboratory animals suggests that a

similar substance might be useful in preventing the development of AD in humans.

NIAID scientists also are conducting test tube studies related to aging. Using a new technique, NIAID researchers have isolated almost all classes of stem cells (the earliest developmental form of blood cells) from mouse bone marrow. This isolation process does not appear to alter the cells' normal behavior, suggesting that stem cells are reliable for studying normal blood cell development. Isolated stem cells now can be used to evaluate the effects of the aging process on blood cell development.



Top of Document

Outlook

Scientists have learned a great deal about AD in the past year. Projects in 1995 will seek to identify the gene on chromosome 14 responsible for one form of early-onset AD and to understand better how ApoE works as a risk factor for AD. More specifically, researchers are interested in learning how ApoE relates to plaques and tangles. Scientists also will look for ways to enhance the use of imaging techniques, especially MRI, as early diagnostic or predictive tools for AD. Improved MRI technology is expected to allow researchers to identify initial changes in the hippocampus in AD. PET scans eventually may detect changes in brain metabolism that precede AD onset by as many as 20 years. PET scans also may monitor possible drug therapies that could prevent the severe nerve damage and memory loss that occur in AD patients. Clinical studies of estrogen and anti-inflammatory agents will build on evidence gained from previous epidemiologic studies. Another important area of research in the next few years will focus on behavioral interventions for patients and training programs for caregivers. Taken together, these avenues of research will help scientists to understand the causes of AD to diagnose the disease earlier, and to improve treatment and caregiving strategies.

Published in May 1995



Top of Document



Home Page