2010 ALZHEIMER'S DISEASE PROGRESS REPORT

A Deeper Understanding

U.S. Department of
Health and Human Services

The National Institute on Aging (NIA), part of the Federal Government's National Institutes of Health (NIH) at the U.S. Department of Health and Human Services, has primary responsibility for basic, clinical, behavioral, and social research in Alzheimer's disease, aimed at finding ways to treat and, ultimately, prevent this disease. The Institute's Alzheimer's disease research program is integral to its mission, which is to enhance the health and well-being of older people. This *2010 Progress Report on Alzheimer's Disease* summarizes recent Alzheimer's research conducted or supported by the NIA and other components of NIH, including:

- Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD)—pages 22, 23, 32, and 47
- National Cancer Institute (NCI)—pages 21, 27, 34, 36, 37, and 47
- National Center for Complementary and Alternative Medicine (NCCAM)—page 37
- National Center for Research Resources (NCRR)—pages 18, 19, 21, 22, 23, 24, 25, 28, 31, 35, 36, 38, and 39
- National Eye Institute (NEI)—page 28
- National Heart, Lung, and Blood Institute (NHLBI)—pages 17, 18, 19, 21, 24, 28, 30, 31, 32, 39, and 56
- National Human Genome Research Institute (NHGRI)—pages 21 and 24
- National Institute of Allergy and Infectious Diseases (NIAID)—pages 19, 20, and 36
- National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS)—pages 17, 30, and 31
- National Institute of Biomedical Imaging and Bioengineering (NIBIB)—pages 22, 23, and 39
- National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)—pages 20, 25, and 32
- National Institute of Environmental Health Sciences (NIEHS)—pages 17, 32, 40, and 59
- National Institute of General Medical Sciences (NIGMS)—pages 28 and 37
- National Institute of Mental Health (NIMH)—pages 17, 18, 19, 21, 22, 26, 28, 31, 33, 35, 36, 37, 39, 40, 41, 46, 47, 56, and 58
- National Institute of Neurological Disorders and Stroke (NINDS)—pages 18, 20, 21, 22, 25, 26, 27, 28, 30, 36, 37, 38, 39, 40, 41, and 61
- National Institute of Nursing Research (NINR)—pages 17, 56, and 57
- National Institute on Alcohol Abuse and Alcoholism (NIAAA)—page 32
- National Institute on Deafness and Other Communication Disorders (NIDCD)—pages 28 and 42
- National Institute on Drug Abuse (NIDA)—pages 22, 26, and 27
- National Library of Medicine (NLM)—page 39

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table of contents

Introduction 5

Executive Summary 8

A Brief Primer on Alzheimer's Disease and the Brain 11

2010 Research Advances 15

1 *Estimating the Extent of Alzheimer's Disease* 15

Estimating How Many People Have MCI 16

Dementia Incidence Among the "Oldest Old" 17

2 *Discovering the Genes Behind Alzheimer's Disease* 17

Large Studies Revealing Genetics of Alzheimer's Disease 19

Gene Expression Studies Reveal Proteins Involved in Disorder 19

Imaging the Genetics of Alzheimer's 22

Cognitive Decline and the APOE Gene 23

Animal Studies Describe Roles of ApoE4 Protein 23

Genetic Counseling and Coping with Alzheimer's 24

3 *Understanding the Biology of Alzheimer's Disease* 25

Investigating Changes in Brain Tissue 25

Brain Amyloid: Is It Ever Benign? 26

Imaging "Normal" Brain Aging 26

Cellular Changes in Alzheimer's Disease 27

4 *Determining Risk Factors for Alzheimer's and Cognitive Decline* 29

Links Between Cardiovascular Disease and Cognitive Decline 30

Physical Frailty and Cognitive Decline 30

Exercise and Maintaining Cognitive Health 30

The Role of Diet in Maintaining Cognitive Health 31

Obesity and Risk for Cognitive Decline 32

Vitamin D and Brain Health As We Age 32

Caregiver Stress and Cognitive Health 33

Aging Animals, Stress, and Cognition 33

memory imaging tau beta trials genetics care

table of contents

5 *Developing New Treatments* 33

Beta-Amyloid Directed Therapies 34

Identifying New Therapeutic Targets 35

Testing of Therapeutic Candidates 36

6 *Advances in Detecting Alzheimer's Disease* 38

CSF Biomarkers and Risk Assessment, Diagnosis 39

Imaging the Living Brain 40

Developing New Cognitive Tests 41

Fluctuating Symptoms in Alzheimer's Disease 41

Sensory Changes 42

Motor Changes 42

7 *Testing Therapies to Treat, Delay, or Prevent Alzheimer's Disease* 43

NIA Programs Support Clinical Trials 43

NIA-Funded Clinical Trials 44

Reports from Recently Completed Clinical Trials 45

8 *Advancing Support for Caregivers* 56

Factors in Caregiving and Mortality 56

Reducing Caregiver Stress 56

REACH-ing Out to Caregivers 57

Support for Patient/Caregiver Pairs 57

9 *Examining Social and Economic Risk Factors* 59

Advancing the Future of Alzheimer's Research: NIA Research Infrastructure and Initiatives 60

References 65

Introduction

Alzheimer's disease is an age-related brain disorder that gradually destroys a person's ability to remember, think, learn, and carry out even the simplest of tasks. Alzheimer's is a type of dementia, a broad term for diseases and conditions that damage brain cells and, over time, impair brain function. Alzheimer's is associated with the breakdown of connections between brain cells, or neurons, and their eventual death.

Typically diagnosed in people age 60 and older, in rare cases the disease can occur in people in their 30s and 40s. The first clinical signs of Alzheimer's disease include memory loss or other cognitive problems, such as trouble with language or decision making. As cognition continues to decline, people may also experience disturbing changes in personality and behavior. In the final stage of Alzheimer's dementia, people lose the ability to recognize family and friends and become totally dependent on others for their daily care. Ultimately, Alzheimer's is a terminal illness.

Research shows that Alzheimer's causes changes in the brain years and even decades before the first symptoms appear, so even those who seem free of the disease today may be at risk. The fight against Alzheimer's is urgent because, without a cure or more effective treatment, it will grow increasingly prevalent as the population ages. This report from the National Institute on Aging (NIA), part of the National Institutes of Health (NIH), focuses on the scientists waging that fight, who work each day toward better treatments and, ultimately, prevention of Alzheimer's disease. Their efforts are dedicated to a future free of this devastating disorder. This report details some of their progress toward that goal.

Baby Boomers and the Risk for Alzheimer's

Today, an estimated 2.4 million to 5.1 million people in the United States may have Alzheimer's disease. While estimates of the number of people with the disorder vary, few would dispute the urgent need to find ways to prevent, delay, and treat this age-related disease—especially in light of America's aging population. The U.S. Census Bureau estimates that the 65-and-older population will double to about 72 million during the next 20 years. In fact, in January 2011, America reached a significant milepost when the oldest "baby boomers" turned 65. This trend toward an aging population is accompanied by a sobering reality: studies have shown that the number of people with Alzheimer's doubles for every 5-year interval past age 65. And the ranks of the very elderly, those 85 years and older and at the highest risk for Alzheimer's, are expected to triple by 2050.

To fully appreciate the impact of Alzheimer's disease in America, one must understand its enormous personal and societal costs. Family, friends, and caregivers of people with Alzheimer's experience emotional, physical, and financial stress as they watch a loved one become increasingly forgetful, frustrated, confused, and lost as the disease progresses. Families struggle to care for loved ones at home but often face difficult decisions about

A National Plan to Advance Alzheimer's Research, Care, and Services

In January 2011, Congress passed and President Barack Obama signed into law the National Alzheimer's Project Act (NAPA). The legislation mandates the establishment of a national strategy to oversee, coordinate, and advance Alzheimer's disease research, care, and services. Under the new law, the Secretary of Health and Human Services is charged with leading a national project to:

- Create and maintain a national plan to overcome Alzheimer's disease
- Share information and coordinate research and services across the Federal Government
- Accelerate the development of treatments to prevent, halt, or reverse the course of Alzheimer's
- Improve the early diagnosis and the care and treatment of people with Alzheimer's
- Include racial and ethnic minorities in the plan with an aim to decrease health disparities associated with research, treatment, and services
- Coordinate with international entities in the global fight against Alzheimer's disease

The law established a public-private Advisory Council on Alzheimer's Research, Care, and Services, made up of Federal and non-Federal experts and advocates. The Advisory Council is charged with advising the Secretary in preparing a formal national plan—to be updated annually—to prioritize Federal efforts in research, clinical care, and support services.

The Council comprises 12 Federal agencies, including the Centers for Disease Control and Prevention, Administration on Aging, Department of Veterans Affairs, and Food and Drug Administration. The National Institutes of Health is represented by NIA, which leads the nation's Alzheimer's disease research program. The Council also has a dozen non-Federal members representing Alzheimer's disease advocacy groups, caregivers, healthcare providers, and others. The Advisory Council met for the first time in September 2011.

For more information, please visit the NAPA Web site at *http://aspe.hhs.gov/daltcp/napa/index.shtml.* To view the NAPA law, go to *www.gpo.gov/fdsys/pkg/PLAW-111publ375/pdf/PLAW-111publ375.pdf*

daily, short-term, and long-term care. Frequently, people with Alzheimer's disease rely on assisted living facilities, then nursing homes, for care and support.

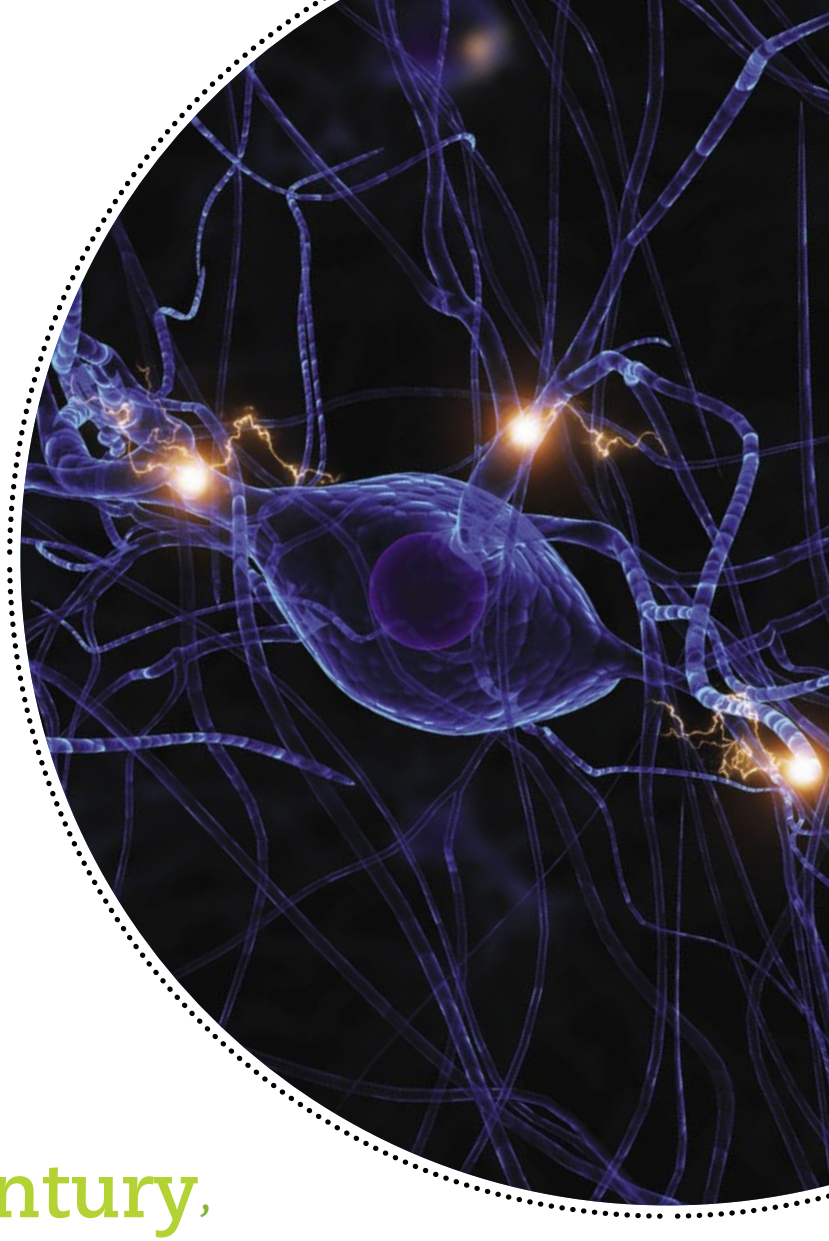
Unless more effective interventions are developed, the number of people living with the disease could escalate significantly, along with the need to support them and their caregivers. That is why researchers and clinicians are devoting their time and talent to developing the interventions needed to help people with Alzheimer's, those at risk for the disease, and the many caregivers on the frontlines of support.

NIH-Supported Research on Alzheimer's Disease

Dr. Alois Alzheimer first described Alzheimer's disease more than 100 years ago. But it was not until the 1970s that researchers began to question the commonly held belief that dementia—or senility, as it was then known—was a normal part of aging. Since then, the scientists

and clinicians who have dedicated their lives to finding the causes of and possible treatments for Alzheimer's disease have greatly advanced our understanding of the disorder. The NIA leads this effort and, with its sister institutes at the NIH, funds and oversees a productive research program into the basic biology of the disease and the factors that influence its development and progression.

The NIH research portfolio covers a broad array of scientific disciplines and seeks to answer complex questions: What are the causes of Alzheimer's disease? How can it be diagnosed early and accurately? How might it be treated? How could it be delayed or even prevented? Over the past quarter century, scientific advances have deepened our insights into this complex disease. While we have much to learn, it is notable that the pace of translational research—which takes laboratory knowledge into the clinical arena—is accelerating. International collaborations are also leading to important discoveries as scientists collect and share the data needed to tease out the genetic variants that may play a role in developing Alzheimer's, and identify and standardize imaging and biomarker measures to better understand the disease's earliest brain changes.



Over the past **quarter century**, *scientific advances have deepened our insights into this* **complex** *disease.*

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Executive Summary

A Deeper Understanding of Alzheimer's Disease

The NIH conducts and supports a balanced program of research that investigates the biological, translational, clinical, behavioral, and societal aspects of Alzheimer's disease, all aimed at improving care, delaying the onset of Alzheimer's disease, and, ultimately, preventing it entirely. Over the past 30 years, since the realization in the late 1970s that Alzheimer's is a distinct disease associated with aging, this research has provided new insights and led to improved scientific methods and tools that are helping to unravel the complexities of Alzheimer's disease and cognitive decline. In recent years, these technologies have allowed researchers to process and analyze vast amounts of data, to look inside the living brain to find Alzheimer's-related changes, and to develop tests that detect disease onset and progression in blood and other biological samples.

Advances in the Biology Underlying Alzheimer's

While two of the hallmarks of Alzheimer's—abnormal levels of amyloid and tau proteins in the brain—have been known for a century, new research is exploring a number of other Alzheimer's-related changes in the brain. Scientists are using imaging to get a clearer picture of the loss of metabolism and connectivity between brain regions, for example. Disruption in the normal functioning of mitochondria—the cell's energy source—is another fruitful area of research. Researchers are also looking at calcium imbalances in the cell to tease out what goes awry in brains that may eventually lead to Alzheimer's disease. (See *Understanding the Biology of Alzheimer's Disease,* page 25.)

Collaborative Studies Reveal Genetics of Alzheimer's

International teams of researchers are working together on genome-wide association studies (GWAS) to identify gene variants that may play a role in the timing of the onset and progression of Alzheimer's disease. In 2010, NIA-funded researchers analyzed brain scans and GWAS data to identify several genes associated with Alzheimer's-related changes in the brain. GWAS enabled a study of how mutated genes regulate proteins, such as beta-amyloid, that may play a role in risk for Alzheimer's. An NIA-led consortium also advanced our understanding of Alzheimer's in a GWAS using DNA data from tens of thousands of volunteers. (See *Large Studies Revealing Genetics of Alzheimer's Disease,* page 19.)

New Guidelines Set for Staging, Diagnosing Alzheimer's

Revised guidelines for measuring Alzheimer's disease progression from presymptomatic stages through dementia reflect our growing understanding of the full course of the disease and its underlying pathology. These new guidelines are primarily directed at testing and validating new concepts in research, but they also update ways for clinicians to assess patient complaints about memory loss and other cognitive changes. Expert panels convened by the NIA and Alzheimer's Association began meeting in 2009 to update the clinical diagnostic criteria for the disease. Completed in April 2011, the National Institute on Aging/Alzheimer's Association Diagnostic Guidelines for Alzheimer's Disease established a new paradigm for diagnosing and researching the disorder.

The original diagnostic criteria, developed 27 years ago, described what we now know are the later stages of Alzheimer's, when symptoms of dementia are already evident. The updated guidelines cover the full spectrum of Alzheimer's as it gradually develops over many years, from the earliest preclinical stages in which symptoms are not evident, to mild cognitive impairment, to dementia due to Alzheimer's pathology. Importantly, the new guidelines address the use, primarily in a research setting, of brain imaging and blood and cerebrospinal fluid biomarkers that may help diagnose Alzheimer's disease at earlier stages. The guidelines are intentionally flexible to allow for changes that could come from emerging technologies and further advances in our understanding of biomarkers and the disease process itself.

For more on the revised guidelines, go to *www.nia.nih.gov/research/dn/alzheimers-diagnostic-guidelines.*

View a short interview of NIA's Dr. Creighton Phelps on the updated Alzheimer's disease diagnostic guidelines.

Identifying Promising Targets for Therapies

Drugs are under development to clear away or reduce the damage thought to be caused by the abnormal accumulation of tau and amyloid proteins in the brain. Other therapeutic targets being researched include compounds such as the SIRT1 and STEP61 enzymes, and substances being tested in animals, such as rapamycin and resveratrol. (See *Developing New Treatments,* page 33.)

Detecting and Diagnosing Alzheimer's

Researchers announced new findings about the relationship between changes in cerebrospinal biomarkers connected to shrinkage in specific brain regions—a pattern that may be an early warning sign of Alzheimer's. They are also exploring how changes in the sense of smell, ability to walk, and other behaviors might signal disease onset. These are just a few ways researchers and clinicians are seeking to identify the earliest signs of Alzheimer's in the brain in order to develop effective interventions. (See *Advances in Detecting Alzheimer's Disease,* page 38.)

Can Lifestyle Factors Delay or Prevent Alzheimer's?

Researchers are exploring several lifestyle factors, from diet and exercise to stress, that may influence age-related cognition and risk for Alzheimer's. In addition to learning more about the connection between heart function and brain health, they are also shedding light on whether the disease mechanisms that play a role in physical frailty also play a role in Alzheimer's. It is possible that reducing high cholesterol, diabetes, and smoking may also reduce the risk of cognitive decline and Alzheimer's. (See *Determining Risk Factors for Alzheimer's and Cognitive Decline,* page 29.)

Testing Therapies in Clinical Trials

A wide array of clinical trials investigating ways to prevent Alzheimer's and cognitive decline are underway. Recently reported results are both promising (a pilot study showed the use of an insulin nasal spray may improve cognition) and disappointing (the largest trial to date testing cholesterol-lowering statins showed they did not improve cognition in people with Alzheimer's). (See *Testing Therapies to Treat, Delay, or Prevent Alzheimer's,* page 43; this section includes a list of ongoing trials and a video on the topic.)

Revised **guidelines** *for measuring Alzheimer's disease progression from presymptomatic stages through dementia reflect our growing* **understanding** *of the full course of the disease and its underlying pathology.*

tau beta imaging clinical risk alpha memory trials biomarkers genetics trials genetics

A Brief Primer on Alzheimer's Disease and the Brain

The healthy human brain is made up of tens of billions of neurons that act as information messengers, transmitting and receiving information via chemical and electrical signals. Glial cells and the brain's rich supply of blood vessels help support and regulate these important activities. Most neurons have three parts: a cell body, an axon, and many dendrites. The cell body contains the nucleus, the cell's genetic blueprint that directs and regulates the cell's activities. The axon, a cable-like structure extending from one end of the neuron, transmits messages. Dendrites, branch-like structures radiating from the other end of the neuron, receive messages.

The function and survival of neurons depends on several key biological processes:

- **Communication**—When one neuron receives messages from another, the cell body generates an electrical charge that travels to the end of the axon. Chemicals called neurotransmitters are released and move across a tiny gap, or synapse, to the dendrites of neighboring neurons. The neurotransmitters bind, or lock into, specific receptor sites, or keyholes, on the dendrites. This action triggers a chemical or electrical charge that either stimulates or inhibits the neighboring neuron's activity. Scientists estimate that one neuron may have as many as 7,000 synaptic connections to other neurons.
- **Metabolism**—This process encompasses all chemical reactions that take place in the cell to maintain life. These reactions require chemical energy in the form of oxygen and glucose, which is supplied by blood circulating through the brain. The brain consumes up to 20 percent of the energy used by the human body, more than any other organ, and has one of the richest blood supplies of any organ.
- **Learning, memory, and repair**—Unlike many short-lived cells in the body, neurons have evolved to live a long time—more than 100 years in humans—so they must constantly maintain and repair themselves. Neurons also continuously remodel themselves—especially as we learn new things—by breaking down synaptic connections with one neighboring neuron and forming new ones with the same cell or even a different neighbor. Research shows that a few brain regions may actually generate new neurons, even as we grow older.

View a short video showing the progression of Alzheimer's disease in the brain.

How Does Alzheimer's Disease Affect the Brain?

While the brain may shrink to some degree in healthy aging, it does not lose neurons in large numbers. In Alzheimer's disease, however, damage is widespread as many neurons stop functioning, lose connections with other neurons, and die. The disease disrupts processes vital to neurons and their networks, including communication, metabolism, and repair.

At first, Alzheimer's disease typically destroys neurons and their connections in parts of the brain involved in memory, including the entorhinal cortex and the hippocampus. It later affects areas in the cerebral cortex responsible for language and reasoning. Eventually, many other areas of the brain are damaged, and a person with Alzheimer's becomes helpless and unresponsive to the outside world.

What Are the Main Characteristics of the Brain with Alzheimer's Disease?

Many changes take place in the brain of a person with Alzheimer's disease. Some of these changes can be observed under the microscope after death. The three abnormalities most evident in the brains of people who have died with the disorder are:

- **Amyloid plaques.** Found in the spaces between neurons, plaques consist predominantly of abnormal deposits of a protein fragment called beta-amyloid. Plaques form when pieces of a protein called amyloid precursor protein (APP) begin to stick together. Plaques also contain other proteins, remnants of degenerating neurons, and other cellular material. Scientists used to think that amyloid plaques were the primary cause of the damage to neurons seen in Alzheimer's. Now, however, many think that other, unclumped forms of beta-amyloid, seen earlier in the plaque formation process, may be the major culprits. Scientists have not yet determined if plaques are a cause or a byproduct of Alzheimer's disease.
- **Neurofibrillary tangles.** Found inside neurons, neurofibrillary tangles are abnormal, insoluble clumps of a protein called tau. Healthy neurons are internally supported in part by structures called microtubules, which help guide nutrients and molecules from the cell body to the end of the axon. Researchers believe that tau binds to and stabilizes microtubules. In Alzheimer's disease, however, tau undergoes abnormal chemical changes that cause it to detach from microtubules and stick to other threads of tau, eventually forming neurofibrillary tangles. The tangles cause the network of microtubules to disintegrate, and the neuron's transport system collapses. As with beta-amyloid, some scientists think that other, smaller forms of abnormal tau may cause the most damage to neurons.
- **Loss of neuronal connections and cell death.** In Alzheimer's disease, the synaptic connections between certain groups of neurons stop functioning and begin to degenerate. This degeneration may be due to abnormal deposits of beta-amyloid and tau. When neurons lose their connections, they cannot function properly and eventually die. As neuronal injury and death spread through the brain, connections between networks of neurons break down, and affected regions begin to shrink in a process called brain atrophy. By the final stage of Alzheimer's, damage is widespread, and brain tissue has shrunk significantly.

What Causes Alzheimer's Disease?

In some rare cases, people develop Alzheimer's in their late 30s, 40s, or 50s. This form of the disease, called "early-onset dominantly-inherited" Alzheimer's disease, often runs in families and is caused by a mutation in one of three genes that a person has inherited from a parent. An NIA-funded clinical study is underway to identify the sequence of brain changes in this form of early-onset Alzheimer's, even before symptoms appear. (See the DIAN study under *NIA Research Infrastructure and Initiatives,* page 63.)

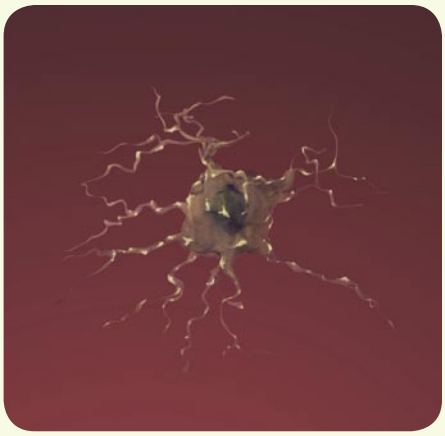
More than 90 percent of Alzheimer's cases occur in people age 60 and older. The development and progression of this "late-onset" form of the disease are very similar to those of the early-onset form of the disorder. The causes of late-onset Alzheimer's are not yet known, but they are believed to include a combination of genetic, environmental, and lifestyle factors. The importance of any one of these factors in increasing or decreasing the risk of developing

Alzheimer's differs from person to person—even between twins.

Much basic research in Alzheimer's disease has focused on the genes that cause early-onset of the disease, and how mutations in these genes disrupt cellular function and lead to disease. Scientists hope that what they learn about early-onset Alzheimer's disease can be applied to the late-onset form of the disease.

Perhaps the greatest mystery is why Alzheimer's disease largely strikes people of advanced age. The single best known risk factor for Alzheimer's is age, and studies show that the prevalence of the disease dramatically increases after age 80. Research on how the brain changes normally as people age will help explain Alzheimer's prevalence in older adults.

Healthy neuron



Dying neuron

How Is Alzheimer's Disease Diagnosed?

Clinicians use a number of tools to diagnose "possible Alzheimer's dementia" (dementia that could be due to another condition) or "probable Alzheimer's dementia" (no other cause of dementia can be found). Some people with memory problems may have mild cognitive impairment (MCI), a condition that may lead to Alzheimer's disease. People with MCI have more memory problems than normal for people their age, but their symptoms are not as severe as those seen in Alzheimer's. Importantly, not all people with MCI go on to develop Alzheimer's disease, and some may even recover from MCI and regain their normal cognition. This recovery may happen if the MCI is due to a medicine's side effect or temporary depression, for example.

Tools for diagnosing probable Alzheimer's disease include a medical history, a physical exam, and tests—preferably over time—that measure memory, language skills, and other abilities related to brain functioning. Information provided by family members or other caregivers about changes in a person's day-to-day function and behavior also help in diagnosis. Currently, a definitive diagnosis of Alzheimer's can be made only after a brain is autopsied after death. However, in specialized research facilities such as the NIA's network of 29 Alzheimer's Disease Centers, clinicians may also use brain scans and biomarkers in blood and cerebrospinal fluid to help diagnose Alzheimer's dementia in people who may or may not be participating in a clinical trial.

Early, accurate diagnosis is crucial because it tells people whether they have Alzheimer's or whether their symptoms are caused by something else. Stroke, tumor, Parkinson's disease, sleep disturbances, or side effects of medications are all known to affect cognitive function and memory, and some of these conditions are reversible. When Alzheimer's is diagnosed, knowing early on can help families plan for the future while the person with the disorder can still participate in making decisions. Researchers are developing tests using biomarkers to detect the disease before memory loss or cognitive impairment is evident. One day these tests could be used in general medical practice.

How Is Alzheimer's Disease Treated?

Only a few medications have been approved by the U.S. Food and Drug Administration to help control the cognitive loss that characterizes Alzheimer's disease. Donepezil (Aricept®), rivastigmine (Exelon®), and galantamine (Razadyne®, formerly known as

Reminyl®) are prescribed to treat mild to moderate Alzheimer's symptoms. Donepezil also is approved to treat severe Alzheimer's.

These drugs act by stopping or slowing the action of acetylcholinesterase, an enzyme that breaks down acetylcholine (a neurotransmitter that helps in memory formation). They maintain some patients' abilities to carry out everyday activities and may slow down symptoms related to thinking, memory, or speaking skills. They also may help with certain behavioral symptoms. However, they do not stop or reverse the underlying disease process and help some patients only for months to a couple of years.

Another type of medication, memantine (Namenda®), is prescribed to treat moderate to severe Alzheimer's symptoms. This drug appears to work by blocking receptors for glutamate, another neurotransmitter involved in memory function. Studies in animals suggest that memantine may have disease-modifying effects, although this effect has not yet been demonstrated in humans.

In addition to these medications, physicians may use other drugs and nondrug approaches to treat behavioral and psychiatric problems associated with Alzheimer's. These problems include agitation, verbal and physical aggression, wandering, depression, sleep disturbances, and delusions. (It is important to note that since no drugs are specifically approved by the U.S. Food and Drug Administration to treat behavioral or psychiatric symptoms in dementia, this practice constitutes "off-label" usage.)

NIA's ADEAR Center Offers Free Alzheimer's Information and Resources

Efforts to educate and inform people with Alzheimer's, their families, the public, providers, and others interested in the disease complement NIH's research initiatives. The NIA Alzheimer's Disease Education and Referral (ADEAR) Center provides free information and publications for families, caregivers, and professionals on research, diagnosis, treatment, patient care, caregiver needs, long-term care, and education and training related to Alzheimer's. For example, the publication *Alzheimer's Disease: Unraveling the Mystery* explains the disease, highlights ongoing research, and describes efforts to support caregivers of people with the disease. An animated companion video brings to life the latest knowledge about Alzheimer's and the brain.

Other ADEAR Center publications include *Caring for a Person with Alzheimer's Disease: Your Easy-to-Use Guide from the National Institute on Aging,* which provides caregiving information and advice. ADEAR fact sheets cover a variety of topics, including basic information, Alzheimer's genetics, and participating in clinical trials and studies. Many ADEAR publications also are available in Spanish.

ADEAR staff members answer telephone, email, and written requests and can suggest local and national resources. In addition, the ADEAR Center Web site offers email alerts, an Alzheimer's clinical trials database, and the Alzheimer's Disease Library database.

To read and order these publications, view the video, and take advantage of many other resources, visit the ADEAR Center at *www.nia.nih.gov/alzheimers* or call the Center toll-free at 1-800-438-4380.

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2010 Research Advances

The NIA/NIH scientific portfolio for Alzheimer's disease covers a wide range of disciplines and research programs. Research conducted and supported by NIH is deepening our understanding of this complex neurodegenerative disorder. This research will help researchers develop new and more effective strategies for delaying and ultimately preventing Alzheimer's and cognitive impairment.

Highlights of studies in 2010 focus on:

1 Estimating the Extent of Alzheimer's Disease
2 Discovering the Genes Behind Alzheimer's Disease
3 Understanding the Biology of Alzheimer's Disease
4 Determining Risk Factors for Alzheimer's and Cognitive Decline
5 Developing New Treatments
6 Advances in Detecting Alzheimer's Disease
7 Testing Therapies to Treat, Delay, or Prevent Alzheimer's Disease
8 Advancing Support for Caregivers
9 Examining Social and Economic Risk Factors

1 Estimating the Extent of Alzheimer's Disease

New and effective ways to prevent, delay, and treat Alzheimer's disease are urgently needed. Today, as many as 5.1 million Americans have the disorder, and its financial and societal burden on individuals and society is expected to rise along with the number of older adults.

Preparing for this challenge from a public health standpoint requires a clear grasp of the numbers involved—how many people are currently affected by Alzheimer's, how prevalence may vary in different socio-economic groups, and likely future trends. Researchers focused on the epidemiology of Alzheimer's disease—or the study of disease in a population setting—met in 2009 to examine the best way to measure prevalence.

Researchers attending the NIA Workshop on Prevalence and Trends considered current peer-reviewed estimates of Alzheimer's prevalence (between 2.4 to 5.1 million people in the United States). They wanted to understand why estimates vary and whether the higher

and lower estimates are useful indicators of the scope of Alzheimer's disease (Anderson and Brayne, eds., 2011).

They determined that the higher prevalence figure of 5.1 million primarily includes people with mild Alzheimer's disease who still function fairly normally. This figure would prove useful, for example, in determining the size of the market for an effective therapy that targets the early stages of the disease. The lower figure of 2.4 million includes people who have moderate to severe Alzheimer's disease and who depend on others for help with daily living. This estimate could be useful in public health planning for more intense resource needs in Alzheimer's caregiving.

Estimating How Many People Have MCI

Mild cognitive impairment, or MCI, is now widely accepted as a possible precursor stage in Alzheimer's disease when symptoms of memory loss are first noticeable. Partly because people with MCI continue to function fairly normally, it remains unclear how common the condition is in the aging population. However, obtaining estimates for MCI prevalence is important for two reasons. First, while people with MCI do not always develop Alzheimer's, they are at greater risk. Second, although people with MCI require less care from their families and health professionals than do people with Alzheimer's dementia, there are costs associated with the condition. Scientists increasingly believe that developing and testing early interventions in people with MCI may be one way to find effective treatments that delay or prevent the symptoms of Alzheimer's disease.

Past estimates of MCI prevalence have come mostly from clinic-based studies. These data may be influenced by the fact that people who come to the clinic may dif-

Prevalence versus incidence—what do the numbers mean?

Epidemiology is the scientific discipline that investigates the distribution of disease in human populations. The basic measures are "prevalence" and "incidence." Prevalence, a measure of disease burden, is a count of the number of people with the disease in a given population at a specific point in time. Prevalence can also be represented as a proportion, or percentage. Incidence pertains to the number of people who acquire the disease during a given interval of time, such as a year. Usually presented as a rate, incidence is a direct measure of disease risk—higher incidence implies higher risk (Ganguli and Kukull, 2010; Brayne et al., 2011).

Estimates of the prevalence and incidence of Alzheimer's disease depend on how broadly or narrowly the condition is defined. Current estimates can be considered low in the sense that only people with clinically obvious disease are included. In particular, higher estimates in the general population tend to come from studies that embrace a broader range of the disease spectrum, from mild to severe cases of Alzheimer's disease.

Epidemiology is also concerned with identifying determinants or predictors of future disease. Some predictors of Alzheimer's disease may in fact be early signs or markers of the disease. Others are independent risk factors, such as a lifestyle factor whose presence or absence is associated with a reduced or increased likelihood that the disease process will commence. The risk factors associated with Alzheimer's and cognitive impairment from epidemiological studies are of most interest as they can uncover potential targets for interventional studies.

fer from those who don't, for example, by being more aware of their cognitive problems or better able to afford care. For that reason, Mayo Clinic-Rochester researchers undertook a "community-based" study of MCI prevalence in Olmsted County, MN, in which they randomly recruited participants (Petersen et al., 2010). Some 16 percent of the nearly 2,000 participants, age 70 to 89, were affected by MCI, the study showed. Among this group, amnestic MCI, in which memory loss is the most prominent feature and the risk for transitioning to Alzheimer's dementia is greater, occurred 2.3 times more frequently than nonamnestic MCI. MCI prevalence was higher in men than women. It was also higher in people who had never married and in those who carried one or two copies of the APOEε4 allele, a known genetic risk factor for late-onset Alzheimer's disease. However, prevalence was lower in those with more years of education.

In another community-based study, University of Pittsburgh researchers used three comparable sets of diagnostic criteria to measure MCI prevalence within a single population (Ganguli et al., 2010). They studied 2,036 people age 65 or older living in small towns in western Pennsylvania. The prevalence of MCI varied, from 18 percent to 36 percent, depending on the measurement used. The researchers noted that the lower figure was calculated using a combination of functional and neuropsychological assessments, while the higher figure employed only neuropsychological assessment. The results of this study indicate that accurate comparison of MCI prevalence in different populations requires researchers to agree on a single set of criteria.

Dementia Incidence Among the "Oldest Old"

Previous research tells us that dementia incidence, or the rate of occurrence of new cases, increases exponentially among people age 65 and 90, doubling approximately every 5 years. Scientists do not know if this doubling continues after age 90, but the answer to this question is critical because the "oldest old," people over age 85, are the fastest growing segment of the U.S. population. Their numbers are expected to grow from 5.5 million to 19 million by 2050.

Researchers at the University of California, Irvine, investigated rates of dementia onset in the advanced elderly (Corrada et al., 2010). Studying 330 cognitively normal participants age 90 and older living in a southern California retirement community, they found that dementia incidence climbed steadily in this group after age 90. Rates ranged from 13 percent new cases per year among those age 90-94 to 41 percent per year in the 100-plus age group, and they continued to almost double with every 5 years of age. Rates of dementia were similar for men and women. Interestingly, preliminary analyses showed no association of dementia in this 90-plus population with risk factors identified in younger age groups, such as history of stroke, heart disease, or the presence of the APOEε4 allele.

Additional references:

- Hebert LE et al. (2010) Change in risk of Alzheimer disease over time. Rush University Medical Center. Supported by NIA, NIEHS, NHLBI, and NINR.
- Borson S et al. (2009) Comorbidity in aging and dementia: scales differ, and the difference matters. University of Washington, Seattle. Supported by NIA and NIMH.

2 Discovering the Genes Behind Alzheimer's Disease

Age is the best known risk factor for cognitive decline and Alzheimer's disease. Age aside, some groups of people appear to be more vulnerable than others. To test new treatments to prevent or delay the onset of the disorder, it will be essential to identify people who are at high risk of Alzheimer's disease but do not show signs of cognitive impairment. This way, interventions can be targeted to those most likely to benefit. Research on Alzheimer's risk factors is offering new insights into the genetics and underlying biology of the disorder beyond the amyloid hypothesis, suggesting new mechanisms and possible targets for drug development.

Children of Parents with Late-Onset Alzheimer's: Who's at Risk?

We know that rare, early-onset familial Alzheimer's disease runs in specific families. But children with a parent with the more common, sporadic form of the disease—called late-onset Alzheimer's—often share an understandable concern about their risk for developing the disease. Indeed, while age is the most common risk factor for late-onset Alzheimer's, having one or both parents with the disorder comes second.

Researchers study the adult children of parents with late-onset Alzheimer's because they have a higher risk of developing the disease. Following these participants before they may develop clinical symptoms of Alzheimer's increases the chances of identifying relevant biological signs (biomarkers) of the disease. Scientists are looking at biomarkers in cerebrospinal fluid (CSF) and blood and tracking brain changes through neuroimaging.

Teams at Boston University, New York University School of Medicine, and William S. Middleton Memorial Veterans Hospital in Madison, WI, used a variety of measures to see if they could detect early signs of brain degeneration in cognitively normal study participants with an average age of 57 to 61. They found that children who had a parent with late-onset Alzheimer's were more likely than those without an Alzheimer's parent to show Alzheimer's-associated changes on brain scans and in two biomarkers (Mosconi, Rinne et al., 2010).

In the New York study, the adult children of parents with late-onset Alzheimer's, particularly those with affected mothers, had higher levels of amyloid deposition in certain brain regions vulnerable to Alzheimer's compared with those without a parental history (Mosconi, Berti, et al., 2010). The Boston University group found that children of parents with late-onset Alzheimer's who were APOEε4-positive also scored lower on memory tests (Debette et al., 2009). Their memory performance was poor for their age, and they had a higher rate of brain atrophy.

Alzheimer's disease is more common in people whose mothers had the disease than in those whose fathers had it. Researchers found evidence of this possible "maternal effect" in cognitively normal adult children of parents with late-onset Alzheimer's. A University of Kansas group found that cognitively normal adults (average age 74) whose mothers had late-onset Alzheimer's were more likely to show Alzheimer's-like patterns of brain shrinkage than those whose fathers had the disease (Honea et al., 2010). In the studies of middle-aged adults described above, people with a maternal history of late-onset Alzheimer's were also more likely to show Alzheimer's-like brain and CSF biomarker changes as well as reduced memory-test performance. In fact, in some tests, people whose fathers had late-onset Alzheimer's did not differ significantly from people who did not have a parent with Alzheimer's.

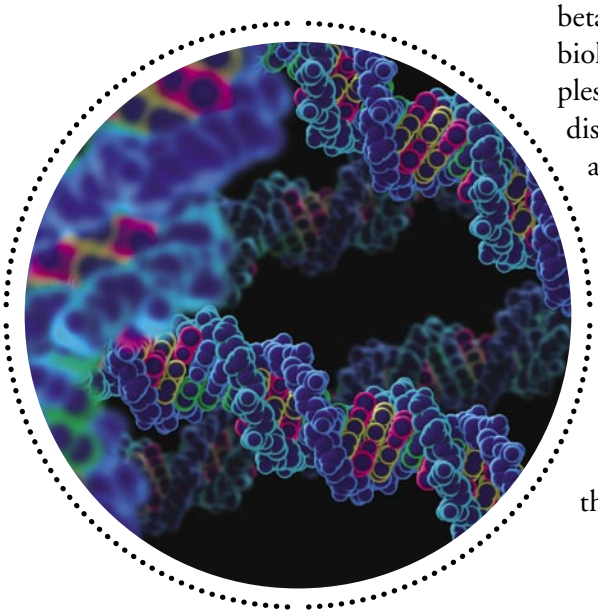
Scientists cite some possible explanations for these findings. One has to do with the phenomenon of genetic "imprinting." People inherit two copies of their genes—one from their mother and one from their father. Usually, both copies of each gene are active, or "turned on." But in less than 1 percent of genes, the copy from the father is "turned off" while the copy from the mother is active. While Alzheimer's disease is not linked to the female, or X, chromosome, there may be genes on the X chromosome contributing to neuronal vulnerability and dementia risk. Lastly, we inherit mitochondria—the part of each cell that converts food into chemicals that power the cell—exclusively from our mothers. If a mother passes on the genetic code for faulty mitochondrial function, her children could be at increased risk for late-onset Alzheimer's.

Additional references:

- Mosconi L et al. (2010) Oxidative stress and amyloid-beta pathology in normal individuals with a maternal history of Alzheimer's. New York University School of Medicine. Supported by NIA and NCRR.
- Bendlin BB et al. (2010) White matter is altered with parental history of Alzheimer's disease. William S. Middleton Memorial Veterans Hospital. Supported by NIA and NIMH.

Large Studies Revealing Genetics of Alzheimer's Disease

After age, inheritance is the biggest risk factor associated with Alzheimer's disease. Efforts to identify genes that play a role have gathered considerable momentum during the past 2 years, thanks primarily to several GWAS involving investigators around the world. Those studies resulted in the identification of the first candidate genetic risk factors for late-onset Alzheimer's to be discovered since 1992, when APOEε4 was first associated with the disease. In 2010, these recent successes were confirmed and expanded when studies identified additional candidate genes emerging from even larger-scale analyses. Other new candidate Alzheimer's risk genes have emerged from studies combining brain imaging and genetics.



Gene Expression Studies Reveal Proteins Involved in Disorder

In some cases, a disease-causing mutation may lie not within a gene itself, but in a nearby region of DNA that regulates gene expression (see *What is gene expression?*). Researchers at the Mayo Clinic, Rochester, MN, looked for mutations affecting the expression activity of 12 candidate Alzheimer's disease genes (Zou et al., 2010). In a GWAS examining postmortem brain tissue from 200 people who had Alzheimer's dementia, they looked for gene variants associated with individual differences in gene expression levels. They identified three single-nucleotide polymorphisms (see *What is a SNP?*, page 22) associated with increased expression of the insulin degrading enzyme (IDE) gene, which reduce levels of beta-amyloid proteins in the brain. Consistent with that biological role, GWAS analysis of more than 4,500 samples from people with Alzheimer's and those free of the disorder showed one of the IDE-linked SNPs to be associated with reduced risk of the disorder.

Genes involved in specific cellular processes (sugar metabolism, for example) tend to be switched on and off together in groups. In one study, University of California, Los Angeles, researchers identified "modules," or clusters of genes likely to be involved in similar cellular processes (Miller JA et al., 2010). In the genomes of humans and mice, the researchers identified and then compared the organization of gene modules in

WHAT IS GENE EXPRESSION?

In gene expression, the information encoded in a gene is switched on at a certain time to direct the assembly of a specific protein. Proteins are required for the structure, function, and regulation of cells, tissues, and organs.

WHAT IS A GENOME?

Every human being is unique, in part because we each carry a unique genome. The genome is the complete set of DNA (deoxyribonucleic acid), the chemical compound that resides within each cell and contains the instructions necessary to build cells and direct their activities. The genomes of any two humans are 99 percent alike, but the 1 percent of variation is critical. It is this variation that creates differences among individuals in eye, skin, hair color, and the shapes of our bodies and faces. Genetic variation also contributes to individual differences in internal physiology, including the risk of developing certain diseases.

the two species. Some modules are very similar in mice and humans—for example, modules that regulate energy metabolism include pretty much the same groups of genes.

The researchers then looked for modules that differed significantly in humans versus mice. They identified one that was both unique to humans and included genes known to be turned on or off in Alzheimer's disease. This module contained not only known Alzheimer's-relevant genes, but also genes not previously suspected to be involved in the disorder. These newly uncovered genes may therefore be "team players" in the disease process, including genes involved in protecting the brain's white matter. The finding is particularly intriguing given increasing evidence that degeneration of white matter occurs in specific brain regions. (Also see Kuczynski et al., 2010)

Additional references:

- Lipinski MM et al. (2010) Genome-wide analysis reveals mechanisms modulating autophagy in normal brain aging and in Alzheimer's disease. Harvard Medical School. Supported by NIA, NIAID, NIDDK, and NINDS.

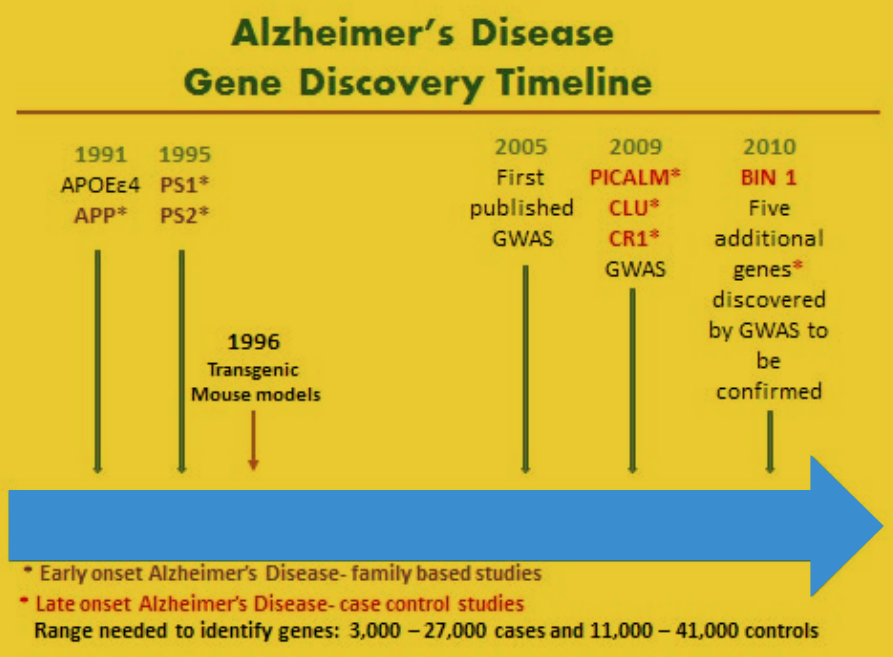
- Thambisetty M et al. (2010) Association of plasma clusterin concentration with severity, pathology, and progression in Alzheimer disease. King's College, London. Supported by NIA.

How Genome-wide Association Studies Advance Research

Individual risk for developing the common, late-onset form of Alzheimer's disease is believed to be influenced by variations in specific genes. Scientists hunt for those genes by comparing the genomes (see *What is a genome?*, page 19) of people who develop the disease with those of people who do not. However, it has become increasingly clear that while many genes influence the risk of late-onset Alzheimer's, most of them (other than APOE) increase risk by only a small percent. Such genes are elusive quarry: finding them requires searching through millions of bits of DNA in samples obtained from thousands of people.

Recent technological breakthroughs have made such genome-wide association studies (GWAS) possible. In GWAS, DNA samples are placed on tiny chips and scanned on automated laboratory machines, which can rapidly analyze large numbers of samples at specific sites within the genome known to show high levels of variability in humans. To accelerate the use of this large-scale technology for the study of late-onset Alzheimer's, the NIA in 2009 established the Alzheimer's Disease Genetic Consortium (ADGC). The ADGC also supports collaborations—worldwide—among Alzheimer's disease genetics researchers to promote the sharing of technical and data resources.

The idea propelling GWAS is that power lies in numbers—not only in bits of DNA analyzed per study participant, but also in the number of participants per study. ADGC-led GWAS published in 2009 included up to 4,000 people with Alzheimer's disease and 8,000 controls, leading to the discovery of three new



late-onset Alzheimer's disease risk-factor genes (PICALM, CLU, and CR1). Numbers of participants are crucial to the discovery of still more Alzheimer's risk-factor genes. ADGC researchers analyzed three different sets of DNA data obtained from 56,000 study participants and found variations in an additional four genes (CD2AP, MS4A4/MS4A6E, EPHA1, and CD33) to be associated with greater risk of Alzheimer's disease. In that study, the largest to date, the ADGC confirmed four genes—CR1, CLU, BIN1, and PICALM—that were discovered in earlier GWAS completed in 2009 and 2010.

More challenges remain: finding other risk-factor genes for late-onset Alzheimer's and making sense of the most recent GWAS discoveries. GWAS discoveries reveal associations between specific single-nucleotide polymorphisms and disease risk, and scientists can make educated guesses about which gene is associated with a particular SNP. However, additional analyses are required to confirm those guesses. Then, the real work begins. Having established that a particular gene increases risk for developing Alzheimer's, scientists study that gene (and the protein it encodes) in cultured cells and animal models to understand its function and how disruption of that function might lead to disease.

Fortunately, we already know about the functions of the newly discovered genes, and subsets of them appear to be involved in common biological pathways, such as lipid processing, immune responses, and cell membrane function and maintenance. GWAS discoveries are providing not only new genes to study, but also broader insights into what biological processes are likely to be disrupted in Alzheimer's disease.

Additional references:

- Jones L et al. (2010) Genetic evidence implicates the immune system and cholesterol metabolism in the aetiology of Alzheimer's disease. Cardiff University School of Medicine, Cardiff, UK. Supported by NIA.
- Jun G et al. (2010) Meta-analysis confirms CR1, CLU, and PICALM as Alzheimer disease risk loci and reveals interactions with APOE genotypes. University of Pennsylvania School of Medicine. Supported by NIA, NINDS, NCRR, NHLBI, NHGRI, and NIMH.
- Lambert JC et al. (2010) The CALHM1 P86L polymorphism is a genetic modifier of age at onset in Alzheimer's disease: a meta-analysis study. Institut Pasteur de Lille, Lille, France. Supported by NIA and NINDS.
- Naj AC et al. (2010) Dementia revealed: novel chromosome 6 locus for late-onset Alzheimer disease provides genetic evidence for folate-pathway abnormalities. University of Miami School of Medicine. Supported by NIA and NINDS.
- Naj AC et al. (2011) Common variants at MS4A4/MS4A6E, CD2AP, CD33, and EPHA1 are associated with late-onset Alzheimer's disease. University of Miami John P. Hussman Institute for Human Genomics. Supported by NIA, NHGRI, NCI, NIMH, NCRR, and NINDS.

Imaging the Genetics of Alzheimer's

The structure of the human brain is thought to be influenced by many common genetic variants. In the case of Alzheimer's, these genetic variants play a role in degenerative changes in brain structure that occur in the disease. By identifying such variants, it may be possible to uncover additional risk-factor genes. New technologies are making this discovery possible, as recent advances in neuroimaging enable scientists to compare millimeter by millimeter the brains of people with and without Alzheimer's disease. Scientists can then harness GWAS data to look for genetic variations and link them to structural changes in Alzheimer's brains.

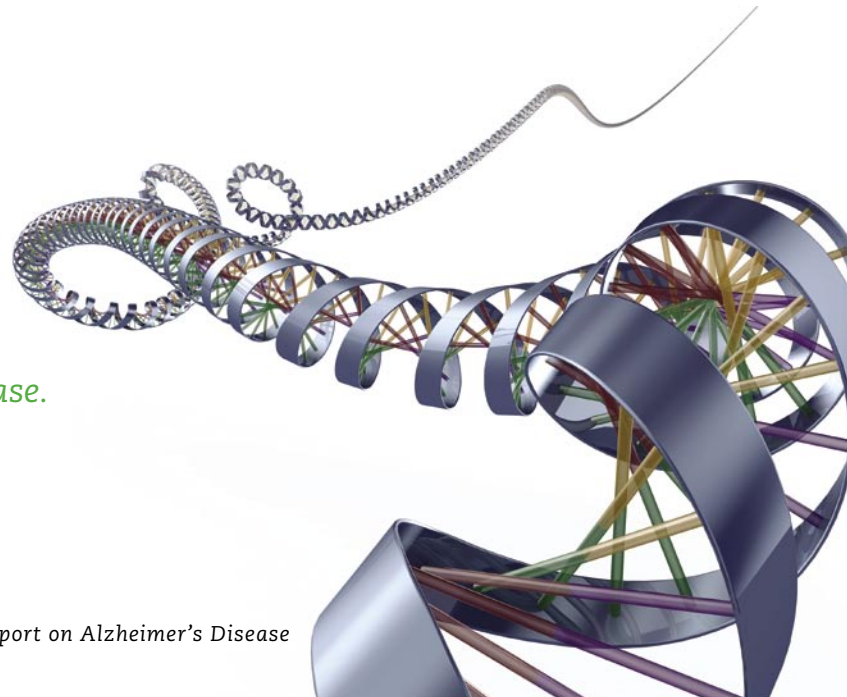
The computational power required for such analyses is enormous (one recent GWAS involved about 100 trillion bytes of data). The Alzheimer's Disease Neuroimaging Initiative (ADNI) helped make this work possible. A public-private partnership led by the NIA, ADNI was launched in 2004 with the goal of identifying Alzheimer's-related structural and functional changes in the brain, as well as standard biomarkers that could predict disease risk and progression. In 2009, ADNI research expanded to embrace the wealth of genetics data coming from GWAS (Saykin et al., 2010). Three papers in 2010 analyzed ADNI data side by side with GWAS data in search of possible candidate Alzheimer's risk-factor genes. (See ADNI details in *Advancing the Future of Alzheimer's Research,* page 62.)

At the University of California, Los Angeles, one group analyzed brain scans using magnetic resonance imaging (MRI) and GWAS data from 742 people with Alzheimer's, MCI, or normal cognition. The study focused on the temporal lobe, the brain region first and most strongly affected in Alzheimer's (Stein, Hua, Morra, et al., 2010). By checking through more than a half million SNPs for each participant, the researchers found one that significantly correlated with temporal lobe shrinkage. The significant SNP was located in the gene GRIN2B. This gene has not previously been implicated in Alzheimer's, so it is not known yet whether it plays a role in disease development. It does, however, play a role in the functioning of receptors for the neurotransmitter glutamate, which affects learning, memory, and the death of neurons. Indeed, this receptor protein is already a target for Alzheimer's treatments. This study shows that coupling brain imaging with genetics might be useful in finding new genetic risk factors.

Scientists at the University of Indiana and University of California, Los Angeles (Shen et al., 2010), undertook even more extensive analyses, examining MRI data from ADNI. The Indiana group identified SNPs in two genes, APOE and TOMM40, which were strongly associated with structural changes in multiple brain regions in people with Alzheimer's. Both of these genes had been previously identified as risk-factor genes for Alzheimer's, but three novel candidate SNPs also emerged from this study. One was especially interesting because it is located near NXPH1, a gene involved in promoting synaptic integrity, or the strength of communications between brain cells. This SNP is also strongly associated with the loss of gray matter in the hippocampus of people with Alzheimer's. A second SNP, EPHA4, is associated with a gene that also influences brain structure. These results suggest links to the mechanisms that may underlie the development and

WHAT IS A SNP?

A SNP, or single-nucleotide polymorphism, is a single change in nucleotides (the building blocks of DNA) that varies from person to person. Researchers use GWAS to identify the variations in SNPs among individuals to find genetic predispositions to health or disease.



progression of Alzheimer's and suggests possible therapeutic targets.

Additional references:

- Kramer PL et al. (2010) Alzheimer disease pathology in cognitively healthy elderly: a genome-wide study. Oregon Health & Science University. Supported by NIA.
- Stein JL et al. (2010) Voxelwise genome-wide association study (vGWAS). University of California, Los Angeles, School of Medicine. Supported by NCRR, NIBIB, NICHD, and NIA.

Cognitive Decline and the APOE Gene

Of the late-onset disease genes discovered to date, the one that confers the most risk is apolipoprotein E, or APOE. This gene, found on chromosome 19, comes in several different forms, or alleles: ε2, ε3, and ε4. The APOEε2 allele is rare, found in 5 to 10 percent of people. APOEε3 is the most common allele, found in about 70 percent to 80 percent of people. Significantly, the APOEε4 allele, found in 10 percent to 15 percent of the gene pool, increases risk for Alzheimer's disease by three- to eight-fold, depending on whether a person has one or two copies of the allele, and is associated with an earlier age of disease onset.

An ongoing question is whether changes in the brain that may lead to cognitive decline differ in people who carry APOEε4 and those who do not. Researchers at the University of California, San Diego, and Brown University in Providence, RI, found that APOEε4 carriers with MCI have more rapid rates of cognitive decline than do noncarriers, as shown by their performance on cognitive tests and/or their ability to carry out normal activities of daily living (Whitehair et al., 2010; Okonkwo et al., 2010). In MRI studies done by the Brown team, decreased brain volumes indicating shrinkage of brain tissue correlated with increased cognitive decline in both APOEε4 carriers and noncarriers. Decreased brain volume was also more evident in APOEε4 carriers than in noncarriers.

Even when deemed cognitively normal, APOEε4 carriers display more signs of age-related brain declines than do noncarriers. In the NIA's Baltimore Longitudinal Study of Aging, 94 participants with a mean age of 69 underwent annual neuropsychological testing and received positron emission tomography (PET) scans to track blood flow in the brain (Thambisetty, Beason-Held et al., 2010). The group included both APOEε4 carriers and noncarriers. Over the course of the 8-year study, the two groups performed equally well on most of the neuropsychological tests. However, the APOEε4 carriers showed more precipitous declines in blood flow in the cortex, an area of the brain that typically declines early in Alzheimer's disease.

These findings may inform the design and interpretation of clinical trials. For example, if treatment and control groups in a trial include people who carry the APOEε4 allele, results may be affected by differences in disease progress between carriers and noncarriers, as well as potential differences in their response to specific treatments.

APOEε2 might be considered the "lucky card" of the three APOE alleles, as it is associated with both reduced risk for Alzheimer's disease and a slower rate of cognitive decline. How APOEε2 benefits the brain is unclear. The relatively small percent of the population who carry at least one copy of the allele may benefit, for example, from slower rates of shrinkage of the hippocampus, a brain region critical for learning and memory. There is also evidence that people with the allele have less buildup of abnormal deposits of beta-amyloid and tau proteins. A University of California, San Francisco, team analyzed rates of hippocampal shrinkage in 134 cognitively normal ADNI participants (Chiang et al., 2010). Over the 2-year study, the hippocampus brain regions of APOEε2 carriers shrank at a much slower rate than in noncarriers. Also, tests of CSF indicated fewer Alzheimer's-like changes in these participants.

Animal Studies Describe Roles of ApoE4 Protein

How the ApoE4 protein increases the brain's susceptibility to Alzheimer's disease remains unknown. We do know that as the protein circulates in the blood, it helps to regulate cholesterol levels and protect against vascular disease. ApoE is also produced in the brain, where it is involved in clearing away beta-amyloid as well as regulating the transport of cholesterol. Animal studies are also uncovering roles for ApoE and other proteins in the development and function of synapses, the tiny structures that connect neurons and enable them to communicate with each other.

Scientists at Georgetown University in Washington, DC, and Duke University in Durham, NC, discovered abnormalities in the synaptic development in mouse models carrying the APOEε4 allele even before the mice

WHAT IS LTP?

LTP, or long-term potentiation, is a process used in research settings to stimulate by mechanical means the connections between neurons in slices of animal brains. LTP studies have shown that the stronger the connection, the better the neurons are able to relay messages across synapses. Researchers theorize that LTP may play a role in learning and memory, but this experimental model has yet to be proved in animals or humans.

reached puberty. Their neurons had fewer dendrites, the branch-like structures that receive messages from other neurons, than those of APOEε3 or APOEε2 model mice (Dumanis et al., 2009). This was associated with less synaptic activity in the amygdala, a brain region important for emotional memory (Klein et al., 2010). In both cases, the deficits were already evident at 1 month of age and progressed as the mice grew older. These studies suggest that while the impact of APOEε4 on cognition is not apparent until later in life, its presence may be harmful to the structure and function of neurons much earlier.

Conversely, the APOEε2 allele associated with decreased risk for Alzheimer's in humans appears to promote synaptic development and, presumably, synaptic function in mice. The neurons of young APOEε2 mice had longer and more elaborate dendrites and as a result, more synaptic contacts than those of APOEε3 or APOEε4 model mice.

The protein ApoE4 may impair synaptic plasticity, or the ability of synapses to weaken or strengthen connections to other synapses—a function critical to learning and memory. When investigators from the University of Texas Southwestern Medical Center added the protein to mice brain segments in the lab, it interfered with the usual chain of cellular responses critical to plasticity, including activity of the protein Reelin, which is involved in plasticity and neuronal function (Chen Y et al., 2010). It particularly affected LTP. This finding could explain the decline in synaptic function seen in both MCI and Alzheimer's disease and suggests a possible target for therapeutic intervention.

Genetic Counseling and Coping with Alzheimer's

People who have parents or siblings with Alzheimer's disease often worry about their risk for developing the disorder. Some seek genetic testing for the APOEε4 risk-factor gene for late-onset disease. It is important to know how people understand and cope with their test results. In particular, scientists are interested in exploring a much-observed phenomenon: while people seem to understand and accurately remember what the clinician tells them about their test results, they still perceive their personal risk differently than it was reported to them.

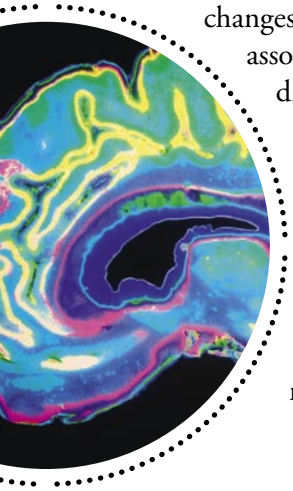
To identify potential sources of this disconnect, University of Michigan researchers studied 246 people who had undergone APOE testing and genetic counseling due a family history of the Alzheimer's (Linnenbringer et al., 2010). They found that 6 weeks after learning their test results, 158 participants accurately recalled the risk estimates provided by the counselor, but nearly half of the group perceived their risk to be different than actually reported: 7 in 10 believed that their chances of developing Alzheimer's disease were significantly higher, while 3 in 10 perceived their risk as lower than the value they'd been given. Notably, some 20 percent of ε4 allele carriers, those with the allele most linked to increased risk of Alzheimer's, perceived a lower lifetime risk of developing the disease.

3 Understanding the Biology of Alzheimer's Disease

Understanding what biological processes go awry in Alzheimer's disease is a key step toward developing treatments. Plaques and tangles are the most obvious postmortem hallmark of the disorder; brain imaging and biomarkers suggest that beta-amyloid is deposited early on in the disease, while tau accumulation occurs later. Research in 2010 offered new insights about how beta-amyloid and tau act and interact to derail synaptic function and kill neurons. However, it has become increasingly clear that the abnormal deposits of these two proteins are not the only molecular culprits in Alzheimer's. Scientists are chasing down other leads and finding out how each may aid and abet beta-amyloid and tau—together or separately—in causing disease.

Investigating Changes in Brain Tissue

A brain damaged by Alzheimer's is characterized by plaques, tangles, neuronal cell death, and degenerative changes in blood vessels. Other abnormal features associated with the disorder continue to be discovered and may provide new diagnostic markers and fresh insights into underlying mechanisms.



For example, studies of how Alzheimer's changes brain structure have generally focused on gray matter, brain regions where neurons and dendrites are found. Deeper in the brain lies white matter, regions that contain large bundles of axons that connect neurons in one region of the brain with neurons in other regions. Because white matter degenerates in people with Alzheimer's, researchers want to know how these changes might relate to changes in gray matter.

Researchers at the University of California, Berkeley, used diffusion tensor imaging to measure the integrity of axons in the white matter of 16 people who ranged from cognitively normal to those with dementia (Kuczynski et al., 2010). The images were then compared to FDG-PET scans showing changes in the participants' brain glucose metabolism. Scientists found that white matter degeneration was linked to reduced metabolism in nearby regions of gray matter, an indicator of decline in neuronal health and function. This finding prompts the question: Do cells in gray matter degenerate first and then damage axons in white matter, or vice versa? Studies investigating white-matter metabolism are underway and may provide new insights into Alzheimer's disease mechanisms.

The accumulation of abnormal amounts of beta-amyloid that occurs in Alzheimer's could result from excessive production of the protein, impaired clearance from the brain, or both. Early-onset Alzheimer's disease involves excess beta-amyloid production, but it is unclear whether the same is true for late-onset Alzheimer's. Researchers at Washington University, St. Louis, developed a method to label beta-amyloid and monitor its turnover in real time in 12 people with Alzheimer's and 12 cognitively normal people of the same age (Mawuenyega et al., 2010). Similar rates of beta-amyloid production were seen in both groups. However, those with Alzheimer's cleared beta-amyloid about 30 percent more slowly than those free of the disease. These data suggest that sluggish clearance of beta-amyloid for a decade or more may

WHAT IS PIB IMAGING?

Researchers can detect abnormal deposits of amyloid protein in the brain by using positron emission tomography (PET) imaging and a tracer, Pittsburgh Compound B (PiB), a radioactive agent specially developed to detect levels of beta-amyloid in the living brain.

contribute to its accumulation in late-onset Alzheimer's. This finding is of particular interest, as most amyloid-related therapies in development so far have targeted production rather than clearance.

Brain Amyloid: Is It Ever Benign?

The advent of PiB imaging brought with it the surprising finding that many cognitively normal older people carry substantial loads of brain amyloid. Is it possible that some people are relatively resistant to the accumulation of brain amyloid and, despite accumulating it, never develop problems with cognitive function?

The answer to that question seems to be a qualified "no." Researchers at Washington University, St. Louis, used PiB imaging to look at 159 cognitively normal people with a mean age of 72 and then tested their cognition for up to 5 years (Morris et al., 2010). Those with higher amounts of beta-amyloid on their initial PiB scans were significantly more likely to develop Alzheimer's symptoms than those who showed little or none.

An NIA-led study found similar results, using PiB imaging to examine 57 people (average age 79) who had undergone annual cognitive testing for the previous 8 to 12 years (Resnick et al., 2010). All had been cognitively normal when they first entered the study but had shown varying degrees of cognitive decline during the subsequent years. PiB scanning showed that the participants with higher brain beta-amyloid levels had also experienced greater losses in cognition and memory during the years prior to their scans.

Finally, a Washington University study of 68 cognitively normal older people and 35 people with Alzheimer's used PiB imaging as well as functional MRI (fMRI), which looks at brain function while doing tasks (Sheline, Morris et al., 2010). Even the cognitively normal people with elevated beta-amyloid levels showed reduced connectivity among brain cells in the default-mode network (brain areas used when the mind "wanders," such as when daydreaming or retrieving memories), compared to individuals with low beta-amyloid. In fact, the disruptions of default-mode network connectivity seen in the cognitively normal participants were similar to those of the people with Alzheimer's disease. Together, these studies suggest that beta-amyloid accumulation signals the presence of preclinical Alzheimer's, even in people free of symptoms.

At the same time, however, evidence shows that some people seem better able to bear the burden of beta-amyloid accumulation than others, despite the likelihood of advancing disease. For some time, scientists have thought this might be due to "cognitive reserve," or an ability of the brain to function effectively despite loss of brain cells or other damage. A number of studies have suggested that higher levels of education and intelligence (as measured on standardized tests) contribute to cognitive reserve and confer some protection against Alzheimer's disease.

Those factors also appear to moderate the effect of beta-amyloid on cognitive function. Researchers at Harvard University, Cambridge, MA, found higher beta-amyloid levels were associated with worse performance on tests of memory, language, vision, and navigation in a study of 66 cognitively normal older people and 17 with Alzheimer's (Rentz et al., 2010). However, elevated beta-amyloid levels had a weaker effect on cognitive function in people who were more highly educated and scored higher on an intelligence test.

Additional reference:

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Imaging "Normal" Brain Aging

Distinctions between age-related cognitive change and change caused by Alzheimer's and other dementias remain an area of debate and intensive research. Dementias are marked by notable declines in cognitive function that reflect underlying brain disease, such as the accumulation of abnormal amounts of plaque and tangles seen in Alzheimer's. Age-related cognitive decline, however, can be more subtle, gradual, and not associated with significant impairments in everyday function.

It is unclear to what extent Alzheimer's-related brain changes may also contribute to "normal" brain aging, especially since PiB imaging has revealed beta-amyloid deposits in a substantial percentage of cognitively normal older people. Indeed, prior to the availability of amyloid imaging, it was impossible to know how many of the older people who participated in previous studies of "normal" aging had some cognitive decline due to the early stages of Alzheimer's or other dementias.

To address this question, researchers at Rush Alzheimer's Disease Center, Chicago, did a postmortem

study of 354 older Catholic nuns, priests, and brothers. The participants had annual clinical and cognitive evaluations starting in 1994 as part of the Religious Orders Study (Wilson, Leurgans, et al., 2010). The scientists found a pattern of gradual age-related cognitive decline, followed by more precipitous decline in the last few years before death (mean age 87). Postmortem findings associated brain tangles and Lewy bodies (pathologies seen in Alzheimer's and Lewy body dementia) with the final stage of decline. Even during the gradual phase of decline, however, some people had significant brain pathology, including tangles, evidence of small or large strokes, and Lewy bodies.

Importantly, those participants who remained cognitively normal to the end had no signs in their brains of Alzheimer's or Lewy body pathology. These observations suggest that neurodegeneration may play a role in the cognitive decline that is often seen in later life. Research is helping us to understand not only the specific effects of various brain changes on cognition, but also the factors that may aid in maintaining normal cognition despite the presence of pathology.

Cellular Changes in Alzheimer's Disease

Calcium Imbalance in Neurons

Scientists have known since 1995 that two gene mutations—presenilin-1 and presenilin-2—cause early-onset Alzheimer's disease, but exactly how is unclear. Because abnormal presenilin proteins are involved in a cascade of events that eventually results in amyloid plaques, previous research has focused on that aspect of presenilin function. However, presenilin mutations also disturb the calcium balance in neurons. Researchers at the University of Texas Southwestern Medical Center, Dallas, have now linked this phenomenon to the development of Alzheimer's-like pathology in mice (Zhang, Sun, et al., 2010).

The researchers studied cultured hippocampal and other brain cells from mouse models with a mutant form of the human presenilin gene. Disabling the presenilin function caused calcium to build up inside the hippocampal cells and prevented the slow release of calcium that is necessary for the health of the cell. In further testing, the researchers blocked other channels the cells might use to release calcium so that the cells could not find other ways to compensate for presenilin dysfunction. This made the Alzheimer's-like pathology even worse. These results unveil a new mechanism explaining how presenilin mutations might lead to the disease. They also suggest that calcium imbalance in neurons may fuel beta-amyloid accumulation and the onset of Alzheimer's.

Additional references:

- Gleichmann M et al. (2012). Molecular changes in brain aging and Alzheimer's disease are mirrored in experimentally silenced cortical neuron networks. Supported by NIA.
- Yang L et al. (2009). Amyloid precursor protein regulates Cav1.2 L-type calcium channel levels and function to influence GABAergic short-term plasticity. Baylor College of Medicine. Supported by NIA.

How Tau Tangles with Neurons

Tangles and other abnormal forms of tau protein accumulate inside the brain cells of people with Alzheimer's. Together with beta-amyloid, they contribute to neurodegeneration. Tangles were long considered the toxic form of tau protein, but increasing evidence points to abnormal forms of soluble tau as more likely suspects. In healthy neurons, soluble tau is concentrated in axons and less abundantly in cell bodies and dendrites. In studying mouse neurons expressing either normal or mutant forms of tau, University of Minnesota, Minneapolis-St. Paul, researchers found that mutant tau ignores its usual cellular boundaries and strays into dendrites, where it accumulates inside spines and interferes with the ability of synapses to communicate via chemical messengers and receptors (Hoover et al., 2010).

The scientists further discovered that mutant tau's movement into dendrites results from excessive (hyper) phosphorylation of the protein. Phosphorylation is a process cells often use to regulate a protein's function or level of activity. Less heavily phosphorylated forms of tau stayed out of dendrites; heavily phosphorylated forms penetrated them more extensively. These findings support other studies pointing to hyperphosphorylated forms of tau as culprits in Alzheimer's disease, and suggest that their toxic effects result in part from disruption of the brain cell's ability to signal other neurons.

Normal as well as mutant forms of tau may contribute to neurodegeneration. For example, in Alzheimer's model mice that accumulate high levels of beta-amyloid, lowering tau levels can reduce damage to brain cells. What role does tau plays in disease progression?

A University of California, San Francisco-led study suggests that tau offers beta-amyloid a foothold in the disruption of axonal transport, a process by which neurons move no longer needed fats, proteins, and other cell parts down their axons and away from the cell body. They looked at how the process differed between cultures of brain cells of normal mice and mice whose tau levels had been reduced or removed. They found the transport of certain cell parts were similar in both normal and tau-deficient neurons—at least until beta-amyloid was added to the mix. With beta-amyloid, the percentage of cell parts being transported dropped by almost half in the normal neurons, but was unchanged in the neurons with reduced tau levels. These results indicate tau interacts with beta-amyloid during axonal transport and may play a role in the toxic effects of Alzheimer's disease (Vossel, 2010).

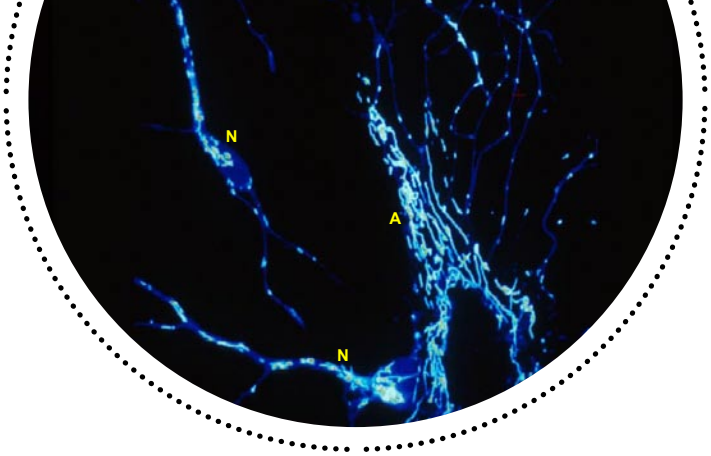
Additional reference:

- Luebke JI et al. (2010) Dendritic vulnerability in neurodegenerative disease: insights from analyses of cortical pyramidal neurons in transgenic mouse models. Boston University School of Medicine. Supported by NIA, NIDCD, and NIMH.

Mitochondria and Energy Disruption

Mitochondria are the parts of the cell that use oxygen to produce energy for the cell via a chemical process. The mitochondria are highly mobile; pushed and pulled by proteins, they travel along a network of protein rods that connect various parts of the cell. Disruption of energy production can be disastrous for cells, as activities grind to a halt without the energy supplied by mitochondria.

Abnormal accumulation of beta-amyloid around neurons may impair mitochondria involved in cell-to-cell communications between synapses. Researchers at Columbia University, New York City, studying Alzheimer's model mice found that beta-amyloid is also deposited *inside* synaptic mitochondria, and that the deposits increased with age (Du, Guo, et al., 2010). Synaptic mitochondria showed impaired energy production, increased vulnerability to damage by calcium, and earlier signs of distress. The scientists also found that low concentrations of beta-amyloid added to mouse neurons in culture slowed the movement of mitochondria up and down axons and decreased their size.



Mitochondrial size was also decreased in neurons treated with beta-amyloid. The findings suggest that synaptic mitochondria appear especially sensitive to injury by beta-amyloid, and their dysfunction may be an early step in the Alzheimer's disease process.

Injury to synaptic mitochondria caused by beta-amyloid may also negatively impact their ability to respond to neurotransmitters, or chemical messengers, in the brain. An Emory University, Atlanta, study showed that beta-amyloid added to neurons in culture could disrupt the movement of energy-vital mitochondria into dendritic spines, a process necessary to stimulate synapses and communication (Rui et al., 2010). At the same time, a type of neurotransmitter receptor—AMPA, which is important to memory formation—failed to function normally. The scientists examined several hundred individual spines and found that spines lacking mitochondria were the same ones that had lost their supply of AMPA receptors. Treating neurons with a compound known to block beta-amyloid suppression of mitochondrial transport reversed this loss. These findings suggest that synaptic mitochondria may be essential for supporting the ongoing supply of AMPA receptors to synaptic membranes, and that function is disrupted by beta-amyloid.

Sometimes cells release free radicals, a molecule (typically oxygen or nitrogen) that can cause damage. While cells maintain complex systems of antioxidants (molecules that block free radicals), a buildup of free radicals may result in a condition known as "oxidative stress." A Baylor College of Medicine, Houston, study suggests that mitochondria may be a major source of the free radicals that cause the oxidative stress typically found in Alzheimer's disease (Massaad et al., 2010). The scientists developed an Alzheimer's disease mouse model that

produces extra high levels of superoxide dismutase-2 (SOD-2), an enzyme that specifically scavenges free radicals produced by mitochondria. Ramping up the levels of this enzyme reversed two Alzheimer's disease-like factors—impaired blood flow in the brain and impaired communication between axons. This study points to free radicals from mitochondria as a major influence in Alzheimer's disease, and suggests that antioxidants specifically targeting them might be explored as possible therapeutics.

Nerve cells use glucose as their main energy source; mitochondria are responsible for converting glucose to energy. When mitochondrial function declines, the function of nerve cells declines, and they are forced to shift to less efficient fuel sources. One factor that may aggravate this decline in mitochondrial function and brain metabolism could be the loss of estrogen experienced during menopause, according to a University of Southern California, Los Angeles, study of female mice (Yao et al., 2010).

The researchers found that the brains of postmenopausal but cognitively normal mice indicated a shift from glucose to alternative energy sources, resembling those of premenopausal Alzheimer's model mice. Meanwhile, the early metabolic changes occurring in Alzheimer's model mice accelerated even further after menopause. These results expand upon previous evidence that estrogen supports mitochondrial use of glucose as a primary energy source and suggest that loss of this support may underlie the increased risk for Alzheimer's disease in menopausal women. They are also consistent with new evidence from human studies that there may be a critical "window of opportunity" around the time of menopause when estrogen therapy may be of cognitive benefit. See *Hormones and Cognitive Health in Postmenopausal Women,* page 47.

Additional references:

- Crews L et al. (2010) Increased BMP6 levels in the brains of Alzheimer's disease patients and APP transgenic mice are accompanied by impaired neurogenesis. University of California, San Diego. Supported by NIA.
- Du H, Yan SS. (2010) Mitochondrial permeability transition pore in Alzheimer's disease: cyclophilin D and amyloid beta. Columbia University College of Physicians and Surgeons. Supported by NIA.
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- Iijima-Ando K et al. (2009) Mitochondrial mislocalization underlies Abeta42-induced neuronal dysfunction in a Drosophila model of Alzheimer's disease. Thomas Jefferson University, Philadelphia. Supported by NIA.
- Sametsky EA et al. (2010) Synaptic strength and postsynaptically silent synapses through advanced aging in rat hippocampal CA1 pyramidal neurons. Northwestern University Feinberg School of Medicine. Supported by NIA.

4 Determining Risk Factors for Alzheimer's and Cognitive Decline

Unlike age and genetics, we potentially can control certain biological and lifestyle factors associated with higher risk of dementia. Scientists are exploring prevention strategies to determine whether or not mental stimulation, exercise, and dietary supplements can delay or reduce the severity of age-related decline or the onset and progression of disease. Additionally, scientists are investigating how certain medical conditions, such as high cholesterol, high blood pressure, and diabetes, influence risk for cognitive decline and Alzheimer's disease.

In April 2010, the NIH convened a State-of-the-Science Conference on Preventing Alzheimer's Disease and Cognitive Decline to review the available scientific evidence and to hear public comment on prevention research. The independent panel of experts charged with this review found that currently no conclusive scientific evidence supports the use of drugs, dietary supplements, or interventions like exercise to reduce risk for the disorder. In its suggestions for areas for scientific exploration, the panel cited promising areas of study, such as ongoing clinical trials testing the usefulness of blood pressure medications, omega-3 fatty acids, physical activity, and cognitive engagement. Many of these interventions are being actively pursued by NIH-funded investigators. To read the panel's final statement and view archived video of the conference, go to *http://consensus.nih.gov/2010/alz.htm.*

Links Between Cardiovascular Disease and Cognitive Decline

Research shows that cerebrovascular disease is a major player in age-related cognitive decline, and that many older people suffer from cerebrovascular disease in addition to Alzheimer's. Some evidence suggests that atherosclerosis, or the buildup of cholesterol and other fatty materials within blood vessel walls, may contribute to the Alzheimer's disease process. If so, perhaps improved control of atherosclerosis could be one way to reduce Alzheimer's risk.

Johns Hopkins University, Baltimore, researchers examined the relationship between atherosclerosis, Alzheimer's pathology (abnormal deposits of plaques and tangles), and dementia in a postmortem study of 200 participants from the NIA's Baltimore Longitudinal Study of Aging (Dolan et al., 2010). Cognitively normal at the beginning of the study, each participant received medical evaluations and cognitive testing for an average of 8.7 years prior to their deaths. While the researchers found no correlation between the presence of atherosclerosis, cerebral mini-strokes, and levels of Alzheimer's pathology—plaques and tangles—in the brains of these individuals, they observed a significant relationship between atherosclerosis and dementia found by cognitive testing. Atherosclerosis of brain blood vessels was calculated to be responsible for 34 percent of the dementia seen in this group. This study suggests that reducing one's exposure to atherosclerosis risk factors, such as high cholesterol, diabetes, and smoking, could be one strategy for reducing risk of dementia.

Heart disease is common in people over age 65. To determine whether there is a relationship between heart function and cognitive aging, researchers at the Framingham Heart Study in Framingham, MA, examined the connection between heart health and brain volume in 1,504 participants, average age 61 (Jefferson et al., 2010). They assessed heart health using the cardiac index, which looks at how much blood the heart pumps per unit of body surface area. Comparing cardiac indexes with brain volumes measured by MRI, the researchers found that people with lower cardiac indexes, those pumping less blood, were more likely to have reduced brain volumes, suggesting they had accelerated brain aging. This correlation was seen even among individuals who did not have clinically evident heart failure. The results suggest that inadequate pumping of blood to the brain could lead to neurodegenerative changes and eventual cognitive decline. Longer-term studies are needed to learn whether people with reduced cardiac function do, in fact, have faster rates of cognitive decline.

Additional reference:

- Iadecola C. (2010) The overlap between neurodegenerative and vascular factors in the pathogenesis of dementia. Weill Cornell Medical College. Supported by NHLBI and NINDS.

Physical Frailty and Cognitive Decline

The physical weakness that often accompanies old age is considered a risk factor for Alzheimer's disease. Physical frailty may also increase risk of developing MCI, according to a Rush Alzheimer's Disease Center, Chicago, study (Boyle et al., 2010). Researchers followed 750 older people from 40 retirement communities in the Chicago metropolitan area, all of whom were cognitively normal at the start of the study. Individuals who were more physically frail, as indicated by lower grip strength and slower walking speed, were significantly more likely to develop MCI over the next 12 years. Together with prior studies showing an association between frailty and Alzheimer's, these data suggest examining whether there may be common disease mechanisms underlying physical frailty and cognitive impairment. In addition, measures of physical frailty may help identify people likely to develop MCI and who might benefit from interventions to maintain cognitive function.

Exercise and Maintaining Cognitive Health

Many observational studies associate physical exercise with successful cognitive aging. Now, a University of California, San Francisco-led epidemiological study suggests that regular exercise during teenage years might be even more effective in boosting cognitive health in old age than exercise in later years (Middleton et al., 2010). Researchers had 9,344 women aged 65 and older (average age 71.6) report their levels of physical activity as

teenagers, at ages 30 and 50, and in late life. Overall, women who were physically active at any age were found to have better cognitive performance and less risk of cognitive impairment in late life than those who were inactive. Those who said they had exercised as teenagers had the best outcomes of all.

Importantly, exercise at any age proved beneficial: Even women who were sedentary teenagers but became more active later had better cognitive function in late life. These findings may suggest that physical activity in early life and ideally throughout life may help reduce risk of age-related cognitive decline.

Brain-derived nerve growth factor (BDNF), a protein produced by brain cells, is essential for both early brain development and healthy brain function in adulthood. BDNF is highly concentrated in the hippocampus, where it supports synaptic plasticity and promotes the generation of new neurons. But serum levels of BDNF decline with age. A University of Illinois at Urbana-Champaign study suggests that loss of circulating BDNF may contribute to age-related cognitive decline (Erickson, Prakash, et al., 2010). In a group of 142 older adults without dementia, increasing age was associated with reduced levels of serum BDNF, smaller hippocampal volumes, and poorer memory performance. Exercise can increase BNDF levels in humans and also has been linked to larger hippocampal volumes and better cognitive function in old age (Middleton et al., 2010). This result suggests that the beneficial effects of exercise on brain function may be gained through its effect on BDNF.

The Role of Diet in Maintaining Cognitive Health

Cholesterol Levels and Risk for Alzheimer's

High cholesterol levels during midlife have been linked to increased risk of developing Alzheimer's disease. University of Arizona, Phoenix, researchers used PET imaging to look at potential links between cholesterol levels and brain metabolism, or the ability of the brain to use oxygen and glucose (Reiman et al., 2010). Brain scans of 117 cognitively normal people aged 53 to 65 showed the brains of people with high cholesterol levels were less efficient in using oxygen and glucose, especially in areas affected by normal aging and Alzheimer's disease. This deficit was more pronounced in carriers of APOEε4. This research suggests that cholesterol may interact with certain Alzheimer's risk factors (including ApoE4, a cholesterol transporter) to increase disease risk, and may also accelerate brain changes that accompany normal aging. This study also points to the potential use of brain scans that measure metabolism as both a way to both predict risk for Alzheimer's in people free of symptoms and to track the effectiveness of treatments in clinical trials.

What Animal Studies Say About "Good" Cholesterol

Apolipoprotein A-1 (ApoA-1) is the main component of high-density lipoprotein (HDL, known as "good" cholesterol). Higher levels of HDL and ApoA-1 are associated with reduced risk for Alzheimer's. Studies from the University of Pittsburgh and University of Illinois, Chicago, suggest that ApoA-1 may prevent the disease by protecting the health of the brain's blood vessels.

In Alzheimer's, abnormal amounts of beta-amyloid accumulate not only around brain cells but in the walls of cerebral blood vessels, leading to impaired cerebral blood flow neuronal function. University of Pittsburgh researchers created an Alzheimer's disease mouse model that lacks the gene for ApoA-1. Compared to Alzheimer's mouse models with an intact ApoA-1 gene, these "knockout" mice developed more significant memory deficits (Lefterov et al., 2010). Examination revealed both models had similar amounts of beta-amyloid deposited in their brains, but the knockout mice had more in the walls of blood vessels. The beta-amyloid accumulation in the vessel walls destroyed the smooth muscle cells that line blood vessels and inhibited their ability to contract and expand and propel blood.

In a complementary study, University of Illinois, Chicago, researchers created Alzheimer's model mice that overproduced human ApoA-1 and, as a result, twice as much "good" cholesterol HDL (Lewis et al., 2010). These mice continued to perform well on tests of learning and memory during aging and showed significantly less beta-amyloid accumulation around their blood vessels compared to normal mice. Together, these two studies suggest that ApoA-1 may benefit cognitive health, in part by preventing and inhibiting the toxic effects of beta-amyloid on brain blood vessels.

What Animal Studies Say About High Fat/Carbohydrate Diets

Saturated fats and refined carbohydrates (such as white sugar) are the main ingredients contributing to weight gain in the modern Western diet. These dietary factors also have been associated with cognitive dysfunction and/or increased risk of Alzheimer's. To learn more about how dietary factors affect brain function, scientists at Purdue University, West Lafayette, IN, fed rats a high-energy diet similar to the one found in Western cultures—high in fats and simple carbohydrates (Kanoski et al., 2010). The results showed that rats fed this high-energy diet for 90 days performed significantly worse on certain memory tests compared to rats fed a diet containing one-third the fat.

Notably, the rats scored poorly on learning and memory tests that require the hippocampus. When the scientists examined the brains of these rats, they found evidence of a breakdown of the blood-brain barrier (BBB) that protects the hippocampus. (The BBB is composed of specialized, protective cells that prevent most molecules and bacteria circulating in the blood from entering and injuring the brain.) Because damage to the BBB was not seen in other regions of the rats' brains, it appeared that the cells of the BBB surrounding the hippocampus were particularly vulnerable to injury as a result of the high-energy diet.

Insulin is a hormone that helps glucose (blood sugar) get into the cells, where it is used as fuel to produce energy. There is growing evidence from human studies that type 2 diabetes, in which a person is deficient in or resistant to insulin, is associated with increased risk for Alzheimer's. This is not surprising given that insulin plays a role in several molecular processes involved in cognitive function.

Researchers at Yale University in New Haven, CT, showed that delivery of insulin to the hippocampus in rodents enhanced memory performance; conversely, blocking insulin function in the hippocampus impaired memory performance (McNay et al., 2010). Insulin delivery into the hippocampus also stimulated local glucose uptake, suggesting that insulin supports memory by generating extra fuel for hippocampal nerve cells. Rats with diabetes symptoms fed a high-fat diet exhibited impaired memory performance compared to rats fed a standard diet. The "diabetic" rats were also resistant to the memory-enhancing and metabolism-boosting benefits of insulin delivered into the hippocampus. These results suggest that impaired delivery and uptake of insulin in the brain may contribute to age-related cognitive decline and increased risk for Alzheimer's.

Additional reference:

- Dieckmann M et al. (2010) Lipoprotein receptors—an evolutionarily ancient multifunctional receptor family. University of Texas Southwestern Medical Center. Supported by NHBLI.

Obesity and Risk for Cognitive Decline

Several human studies have found that being overweight or obese during midlife is associated with reduced cognitive function, markers of brain degeneration, and increased risk of Alzheimer's disease later in life. A University of California, San Francisco, team discovered that older individuals with an elevated body mass index (BMI, a measure of body fat based on height and weight) show metabolic changes in the brain (Gazdzinski et al., 2010). The researchers used a specialized brain scanning technique, proton resonance spectroscopy, to measure levels of N-acetyl-aspartate (NAA), a molecule that reflects metabolic activity of neurons. They found that cognitively normal older people with higher BMIs have lower levels of NAA compared to older people with a normal BMI. While NAA functions are still poorly understood, reduced levels are thought to signal problems in neuronal metabolism and loss of dendrites and axons.

Additional reference:

- de la Monte SM et al. (2010) Ceramide-mediated insulin resistance and impairment of cognitive-motor functions. Rhode Island Hospital. Supported by NIAAA.

Vitamin D and Brain Health As We Age

A significant number of older people in the United States and Europe living in the community may have vitamin D deficiencies, studies show. To determine if vitamin D plays a role in cognitive health, NIA investigators and an international team of researchers followed a group of 858 people age 65 or older living in Tuscany, Italy (Llewellyn et al., 2010). During the 6-year study, subjects who were severely deficient in vitamin D experienced significantly faster rates of cognitive decline than those with adequate levels. This finding adds to

emerging evidence that vitamin D may be important for brain health and function and may protect neurons from damage. Future clinical trials could tell us more directly about the importance of vitamin D, which can be obtained through the diet or sensible sun exposure, in preventing age-related cognitive decline.

Caregiver Stress and Cognitive Health

Spouses often take on much of the burden and stress of caring for loved ones with dementia in a system of "informal," or unpaid, care. Now, a University of Utah, Salt Lake City, study suggests that this type of caregiving also may contribute to the caregiver's own risk of dementia (Norton et al., 2010). The researchers studied a group of 1,221 married couples aged 65 or older, in which both partners were free of dementia at the start of the study and lived together at home. Compared with individuals whose spouses remained dementia-free, people whose spouses were diagnosed with dementia were at six times greater risk of developing dementia within an average of 4 years following the diagnosis. This correlation was not influenced by how long the couple had been married, and husbands had a nearly three-fold greater risk of dementia than their wives.

Further research should help determine whether the chronic and often severe stress associated with dementia caregiving is a major risk factor for the development of dementia in spouse caregivers.

Aging Animals, Stress, and Cognition

Older brains seem less resilient to stress than younger ones, and exposure to stress may accelerate cognitive aging. Rockefeller University, New York City, researchers found that the brains of older rats self-repair less readily after stress (Bloss et al., 2010). In both young and old confined rats, stress caused degenerative changes in an area of the brain vulnerable to aging—the prefrontal cortex, which is vital to planning and decision making. Immediately after a period of stress, the rat brains revealed withered dendrites, with a loss of 20 percent of their branches. By the end of a post-stress recovery period, the dendrites of young rats had returned to their normal lengths and branch numbers, but the dendrites of old rats had not. These observations suggest that neuronal resilience to stress may be lost with age. Certain interventions, including exercise and exposure to more interesting environments, have been found to improve neuronal resilience in aged rodents and might be further explored in humans.

5 Developing New Treatments

The prevalence of Alzheimer's disease is expected to rise with the aging of the population, increasing the urgency to develop new therapies to treat, delay, and, ultimately, prevent the disease. Drugs currently used in treatment include cholinesterase inhibitors and memantine, both of which help support neurotransmitters important to memory function. These drugs provide symptomatic relief and may slow symptoms of cognitive decline for some people for a limited amount of time. But because they do not target underlying molecular pathways believed to be involved in Alzheimer's, they neither halt nor reverse progression of the disease.

Translational research is a multidisciplinary, multistep process that uses basic science discoveries to develop medicines or other interventions that improve human health. The process of discovering and developing new

View a brief video of the NIA's Dr. Suzana Petanceska on the goals and challenges of translational research.

The **prevalence** *of Alzheimer's disease is expected to rise with the aging of the population, increasing the urgency to develop new therapies to* **treat**, **delay**, *and, ultimately,* **prevent** *the disease.*

drugs for neurological disorders like Alzheimer's is extremely challenging and expensive. It takes 10 to 15 years from the discovery of a new therapeutic target until a new drug reaches the market, with an average cost of about $1.8 billion (Paul et al., 2010).

Intensive efforts are underway in translational research to identify and test therapies that interfere with a variety of disease processes involved in the development of Alzheimer's. A range of disease pathways are being explored, from Alzheimer's-related abnormal deposits of amyloid and tau proteins to the potentially protective roles played by growth factor molecules. The NIA supports several innovative programs that foster the preclinical drug development and testing of novel compounds described in this section (see *Advancing the Future of Alzheimer's Research,* page 60). At the same time, the NIA is putting new interventions to the test by supporting and conducting human clinical trials (see *Testing Therapies to Treat, Delay, or Prevent Alzheimer's Disease,* page 43).

Beta-Amyloid Directed Therapies

Efforts to design drugs targeting beta-amyloid have been hindered by uncertainty as to exactly which form or forms of the protein are toxic to neurons—single fragments called monomers, combinations of two or more of the monomers, or still larger groups of fragments, known as aggregates, that eventually form plaques. Researchers at the Broad Institute, Cambridge, MA, sought to move beyond this issue by developing a new method for screening molecules based simply on their ability to bind beta-amyloid monomers (Chen J et al., 2010). They reasoned that regardless of which form of beta-amyloid is toxic, any compound that could block its toxicity would first have to bind to the protein. The researchers prepared small-molecule microarrays—glass slides onto which they bound spots of thousands of different chemical compounds—and then applied fluorescently labeled beta-amyloid to the slides to track where the beta-amyloid latched onto specific spots. In a screen of close to 20,000 compounds, researchers found 79 that bound beta-amyloid; one of these, compound 2002-H20, significantly reduced beta-amyloid toxicity.

Beta-amyloid plaque production involves the cleavage, or cutting, of the larger amyloid precursor protein by two enzymes, beta-secretase and gamma-secretase. While scientists have developed a number of compounds that can block gamma-secretase, completely blocking the enzyme could have negative side effects since it is involved in the processing of many cellular proteins. Researchers at Torrey Pines Therapeutics, La Jolla, CA, and Memorial Sloan Kettering Cancer Center, New York City, looked for "hits" that would block beta-amyloid production without affecting gamma-secretase's cleavage of Notch, a protein important to gastrointestinal health (Kounnas et al., 2010).

The researchers screened more than 80,000 compounds to develop a drug candidate to test. Named "Compound 4," the drug was 1,000 to 10,000 times more potent than tarenflurbil (a leading beta-amyloid buster) in blocking beta-amyloid production by cells in culture. The researchers fed Compound 4 to Alzheimer's model mice for 29 weeks starting at 8 months of age, when beta-amyloid plaques were just starting to accumulate. Compared to the brains of control mice, which were loaded with beta-amyloid plaque, the drug reduced the load two- to three-fold in the treated group. The treated mice were also free of gastrointestinal lesions, showing that Compound 4 did not inhibit the positive role played by gamma-secretase.

Identifying New Therapeutic Targets

The search for new drugs begins with the identification of new therapeutic targets. Each year, NIA-funded researchers discover new molecular players in the Alzheimer's disease process that are potential therapeutic targets. As research on anti-beta-amyloid therapies progresses, there is increasing interest in identifying other possible targets for drug development. After beta-amyloid, the next "most wanted" protein is tau, the focus of a number of drug development efforts. Other new molecular suspects in the Alzheimer's disease process continue to be identified, and some show particular promise as drug targets.

Tau and Tau-Related Targets

Like many proteins, tau may undergo extensive chemical processes during its lifetime inside the cell, the most prominent of which is phosphorylation—the addition of a phosphate group that may switch on or off certain enzymes or receptors. This process can run amok. Tau that is too heavily phosphorylated is toxic to neurons, tends to clump together and form tangles, and may contribute to neurodegeneration in Alzheimer's disease. Researchers have focused on blocking this tau hyperphosphorylation. Now, other cellular mechanisms of tau processing are being uncovered and could provide alternative targets for drug development.

A team at the Gladstone Institute of Neurological Disease/University of California, San Francisco, has discovered that in addition to tau phosphorylation, a process called acetylation (the adding of an acetyl group, usually an acid, into a compound) may contribute to tau damage to neurons (Min et al., 2010). Specifically, acetylation appears to block the cell's ability to destroy worn-out tau molecules, so that toxic forms of tau pile up in the cell. Moreover, increased tau acetylation was seen in neurons treated with beta-amyloid and in postmortem human brains with tau pathology (for example, hyperphosphorylated tau accumulation and tangles). Finally, the researchers identified a brain enzyme, SIRT-1, that can remove acetyl groups from tau. Interestingly, studies this year revealed additional mechanisms whereby SIRT-1 appeared to protect cognitive health, making this enzyme a particularly enticing target for drug development.

Sometimes, the process of folding and packaging proteins fails, resulting in a misfolded or misshapen protein that can damage the cell. However, cells have a quality control mechanism called the unfolded protein response (UPR) that can detect and remove misfolded proteins. The cell then resets its protein making machinery. The UPR mechanism is overly active in the brains of people with Alzheimer's, perhaps as the brain's response to the abnormal accumulation of misfolded proteins.

Harvard University, Cambridge, MA, researchers studying a fruit fly model found that increasing tau expression activated the UPR mechanism and that highly mutant forms of tau further increased UPR activity (Loewen and Feany, 2010). This finding suggests that the UPR mechanism can protect cells from tau neurotoxicity, and that its activation could be explored as a new therapeutic avenue in Alzheimer's disease.

Additional reference:

- Ballatore C et al. (2010). Discovery of brain-penetrant, orally bioavailable aminothienopyridazine inhibitors of tau aggregation. University of Pennsylvania. Supported by NIA.

STEP61 Enzyme

Increasing evidence suggests that disruption of the protein recycling and degradation pathways, which are critical to the health of neurons, may contribute to Alzheimer's disease. A Rockefeller University, New York City, study suggests that beta-amyloid disrupts synaptic function in the hippocampus by blocking the degradation of the enzyme STEP61 (Kurup et al., 2010). STEP61 appears to impair synaptic plasticity in the hippocampus by removing the glutamate receptors necessary for maintaining proper communication between neurons. The scientists found that STEP61 levels are abnormally elevated in the brains of people with Alzheimer's and in Alzheimer's model mice with high levels of beta-amyloid. Laboratory experiments revealed that accumulation of beta-amyloid led to increased levels of STEP61, resulting in the loss of glutamate receptors at the synapse.

In a subsequent study in mouse models with reduced levels of STEP61, the Rockefeller team showed that these mice had restored levels of glutamate receptors and measures of synaptic plasticity (Zhang, Kurup, et al., 2010). This was associated with improved performance on a memory test. These findings suggest that STEP61 could be a therapeutic target for Alzheimer's disease.

SIRT-1

SIRT-1 is an enzyme mostly known as a regulator of lifespan in yeast and worms. In 2010, SIRT-1 emerged as a new candidate drug target for Alzheimer's, based on two new-found possible roles in brain function. In one study, researchers found SIRT-1 was capable of removing damaging acetyl groups from tau and alleviating tau neurotoxicity (Min et al., 2010). Studies led by a team of scientists from the University of Southern California, NIA, Florida, Mexico, and Ontario (Michán et al., 2010) and a team from the Massachusetts Institute of Technology, Cambridge, (Gao et al., 2010) suggested that SIRT-1 is linked to learning and memory in mice. Both teams used mouse models lacking SIRT-1 and observed impaired performance on learning and memory tests, reduced synaptic plasticity, and abnormal branching of hippocampal neurons. The two teams also identified several new molecular pathways through which SIRT-1 may support synaptic plasticity in the hippocampus. Further research will pinpoint which molecules from the pathways could be useful as therapeutic targets for Alzheimer's disease.

Toll-like Receptors

Proteins involved in immune system responses keep popping up with unexpected roles in how brain cells communicate with other neurons. The latest of these proteins are toll-like receptors (TLRs), previously thought to function in the brain only during infection and injury. NIA researchers found that one of these receptors, TLR-3, plays a role in memory retention, apparently unrelated to any immune function (Okun et al., 2010). Significantly, TLR-3 appears to inhibit rather than promote forms of memory that depend on the hippocampus. Mouse models lacking TLR-3 show improved working memory performance, together with increased hippocampal size, increased generation of new hippocampal neurons, and higher levels of signaling molecules required for synaptic plasticity. Control mice with TLR-3 did not display these attributes. At the same time, anxiety-like behavior was diminished in the experimental mice, which performed better than the control mice. More research is needed into how TLR-3 affects memory and learning.

Additional references:

- Douglas PM, Dillin A. (2010) Protein homeostasis and aging in neurodegeneration. Salk Institute for Biological Studies. Supported by NIA.
- Miller TW et al. (2010) Amyloid beta inhibits NO-cGMP signaling in a CD36- and CD47-dependent manner. National Cancer Institute. Supported by NCI.
- Stewart CR et al. (2010) CD36 ligands promote sterile inflammation through assembly of a Toll-like receptor 4 and 6 heterodimer. Harvard Medical School. Supported by NIA, NIAID, and NINDS.

Testing of Therapeutic Candidates

As we learn more about the biology and genetics of Alzheimer's disease, currently available compounds or newly developed agents targeting specific Alzheimer's disease mechanisms are typically tested in animal models before they are tested in human clinical trials. The animal models are usually transgenic mouse models that have been genetically developed to have proteins that function like those thought to be involved in human disease.

In studies conducted in 2010, the following agents were among those that had beneficial effects on Alzheimer's pathology in these animal models:

- ***Resveratrol.*** Several observational studies have associated moderate consumption of red wine with a lower incidence of dementia. Antioxidant compounds found in red wine, including resveratrol, have been shown in animal studies to have neuroprotective effects, and researchers are exploring the mechanisms by which these

compounds may work. In one study, Albert Einstein College of Medicine, Bronx, NY, researchers found that resveratrol lowered beta-amyloid accumulation in cultures of neurons and other cells from Alzheimer's model mice (Vingtdeux et al., 2010). Resveratrol lowered beta-amyloid by increasing calcium levels in cells (depleted calcium levels are linked to the disorder) and by activating an enzyme known as AMPK that triggers the destruction of beta-amyloid. When the scientists fed resveratrol to Alzheimer's model mice, the compound crossed the blood-brain barrier, activated brain AMPK, and reduced beta-amyloid accumulation. These results suggest that resveratrol's ability to reduce brain beta-amyloid levels might explain the beneficial link between wine consumption and cognitive health. They also provide impetus for further study of the therapeutic potential of resveratrol and other compounds that activate AMPK.

- ***Grape seed extracts.*** In related research, Mt. Sinai School of Medicine, New York City, researchers have been studying a grape seed polyphenolic extract (GSPE) rich in certain antioxidant molecules. The scientists found previously that GSPE inhibits the buildup of beta-amyloid. Now, they have discovered that GSPE also strongly interferes with the assembly of tau proteins into neurotoxic clumps in an animal model (Wang, Santa-Maria, et al., 2010). Oral administration of GSPE also reduced tau tangle formation in a tau mouse model, where the beneficial effect of GPSE appeared to affect activation of ERK1/2, an enzyme that promotes the accumulation of toxic forms of tau. This finding suggests that GPSE may be explored as a potential therapeutic target to prevent damage caused by toxic forms of both beta-amyloid and tau.

- ***Glucagon-like peptide-1 (GLP-1).*** This hormone produced in the stomach helps stimulate pancreatic insulin secretion when blood glucose levels rise. Drugs that mimic the hormone are used to treat type 2 diabetes. It appears that activating the GLP-1 receptor may play a role in protecting brain cells, as shown in a study led by the NIA. Researchers discovered that the diabetes drug Exendin-4 activates the GLP-1 receptor and can protect cultured neurons from beta-amyloid toxicity and oxidative stress in Alzheimer's mice models (Li Y et al., 2010). It could also reverse some of the increase in beta-amyloid found in Alzheimer's mice with diabetes. The compound is being tested in humans in a clinical trial.

- ***Rapamycin.*** The mTOR pathway is involved in regulating cell growth, death, and metabolism. Rapamycin, a drug that inhibits mTOR, has been shown to extend lifespan in mice. Two independent teams at the University of Texas Health Science Center, San Antonio, found that rapamycin treatment reduced Alzheimer's-like pathology and prevented cognitive deficits in two different mouse models (Caccamo et al., 2010; Spilman et al., 2010). They showed that rapamycin stimulated the process cells use to digest and clear away waste proteins and other debris. The studies also found that the accumulation of beta-amyloid in cultured cells increased mTOR signaling, while inhibiting mTOR signaling reduced cellular beta-amyloid levels. This result suggests a molecular link between beta-amyloid and mTOR, and that stimulating the cell clearance process could be one therapeutic avenue in Alzheimer's.

- ***Fibrinogen depletion.*** Fibrinogen is a fibrous protein that helps blood clots form. While not normally found in the brain, it accumulates in the brains of people with Alzheimer's and is linked to increased risk for the disorder. Rockefeller University, New York City, scientists found that beta-amyloid can be trapped in the sticky matrix fibrinogen forms during clot formation, producing clots that are more resistant to degradation (Cortes-Canteli et al., 2010). They also found that clots developed more rapidly and persisted longer in the brains of Alzheimer's model mice than in control mice. To further test the impact of such clots, they treated two different Alzheimer's mouse models with ancrod, a protein from Malaysian pit viper venom that reduces blood fibrinogen levels. They found that ancrod treatment reduced the blood clot pathology and improved cognition in the mice. More research must be done to understand amyloid-

related cerebrovascular pathology, but this study suggests the possibility of developing drugs that block the effects of beta-amyloid on clot stability. Because beta-amyloid is found primarily in the brain, such drugs should not influence clot formation elsewhere in the body.

● ***Allopregnanolone.*** This derivative of the female sex hormone progesterone stimulates proliferation of neuron precursors, or developing brain cells. Scientists know that many regions of the brain produce new neurons throughout life, and they speculate that declining neurogenesis contributes to Alzheimer's disease. Consistent with that idea, scientists at the University of California, Los Angeles, found an almost 50 percent reduction in the number of neural cell precursors in the hippocampus of 3-month-old Alzheimer's model mice compared to control mice (Wang, Singh, et al., 2010). This defect in neurogenesis was evident a full 3 months before the Alzheimer's model mice first showed beta-amyloid deposits and impaired performance on a learning task involving the hippocampus. Because the Alzheimer's model mice also had reduced brain levels of allopregnanolone, the scientists treated them with the hormone. A single injection restored neurogenesis in the model mice back to the levels seen in normal mice and also corrected their learning deficit. These results may stimulate interest in allopregnanolone and other treatments that boost neurogenesis as potential Alzheimer's therapeutics.

Additional references:

- Cook JJ et al. (2010) Acute gamma-secretase inhibition of nonhuman primate CNS shifts amyloid precursor protein (APP) metabolism from amyloid-beta production to alternative APP fragments without amyloid-beta rebound. Washington University School of Medicine. Supported by NIA, NCRR, and NINDS.

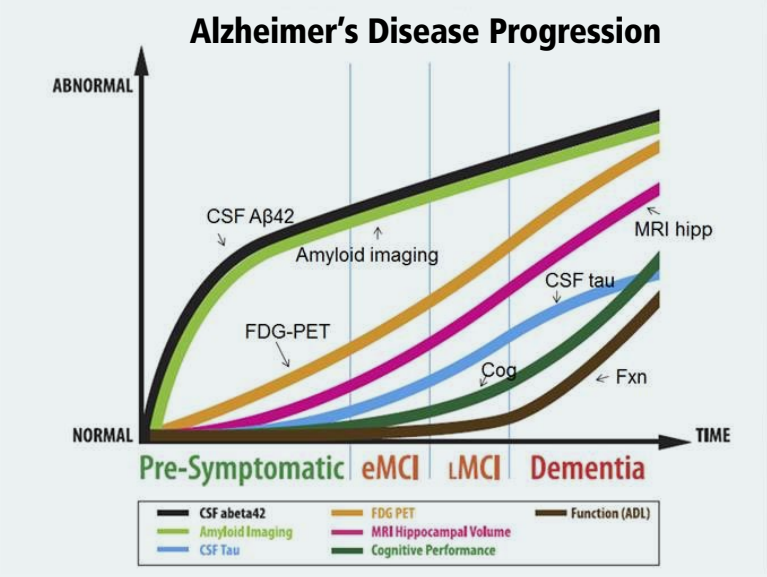
- O'Leary JC III et al. (2010) Phenothiazine-mediated rescue of cognition in tau transgenic mice requires neuroprotection and reduced soluble tau burden. Byrd Alzheimer's Research Institute, University of South Florida. Supported by NIA and NINDS.

6 Advances in Detecting Alzheimer's Disease

Many researchers believe that treatments for Alzheimer's are more likely to be effective if initiated early in the disease. Because scientists believe that changes in the brain leading to Alzheimer's disease can occur one to two decades before cognitive impairment becomes evident, they are trying to develop methods to detect these changes at their earliest stages. In addition, a growing body of research suggests that other early symptoms, including changes in sensory and motor function, may precede memory changes in Alzheimer's. These efforts are designed to determine who is at the highest risk for Alzheimer's so that possible treatments can be tested more rapidly, as well as to improve diagnosis in clinical practice. Through NIA-led ADNI and other studies, these efforts are already showing some success. (See *Advancing the Future of Alzheimer's Research* for more on ADNI, page 62.)

Scientists are currently exploring three main approaches to early diagnosis: measurements of CSF biomarkers, brain imaging, and standardized clinical tests of memory and thinking abilities to determine cognitive health.

View a brief video of the NIA's Dr. Laurie Ryan on the Alzheimer's Disease Neuroimaging Initiative (ADNI), a novel effort to identify biomarkers.



This diagram illustrates how Alzheimer's-related changes in the brain may contribute to disease progression, from normal cognitive aging to early mild cognitive impairment (eMCI) to late MCI (LMCI) and to Alzheimer's dementia. The curves represent the sequence in which specific markers may play a role in disease progression. This model suggests that different imaging tools, measurements, and biochemical biomarkers may serve as predictors (measures that predict future change) and outcomes (measures that detect change) at different stages in the transition from normal aging to MCI to dementia. The NIA-led ADNI study (see page 62) is gathering data to test this model.

CSF Biomarkers and Risk Assessment, Diagnosis

Using CSF biomarkers to diagnose and track the progress of Alzheimer's disease is an increasingly productive area of research. Previous studies showed that changes in CSF levels of three proteins (beta-amyloid 1-42, tau, and phosphorylated tau) can, in a controlled experimental setting, reliably identify individuals with Alzheimer's (Jack, Knopman, et al., 2010).

Brain imaging has built upon and complemented that advance by detecting both amyloid accumulation and neurodegeneration, suggesting that it may be possible to identify individuals at risk for Alzheimer's well before the disease is clinically apparent. Recent studies have focused on a number of questions: How do changes in levels of CSF biomarkers relate to structural changes occurring in the brain? Can CSF biomarkers be used not only to diagnose Alzheimer's but also to identify individuals at risk? Are CSF biomarker changes more or less accurate predictors of cognitive decline than brain structural changes detectable by brain imaging?

Independent teams at the University of California, Los Angeles; the Department of Veterans Affairs, San Francisco; and the University of Oslo used data from ADNI to find that changes in specific CSF biomarkers could be linked to shrinkage of specific brain regions that degenerate in Alzheimer's (Apostolova et al., 2010; Tosun et al., 2010; Fjell et al., 2010). However, they found that the relationships between CSF biomarker and brain structural changes were not entirely straightforward.

In the Oslo study, for example, MCI patients showed more degeneration in some brain regions than would have been predicted by their CSF marker levels compared to control subjects. In addition, both the San Francisco and UCLA groups found that patterns of CSF marker changes relative to brain structural changes differed, depending on the individual's stage of disease. The relationship between genetic risk factors and CSF biomarkers and imaging was difficult to discern since it varied by brain region and clinical group (cognitively normal, MCI, or Alzheimer's). While an individual's CSF marker profile alone does not provide a perfect snapshot of degenerative changes taking place in the brain, these results suggest the emergence of patterns in certain biomarkers that, with measures of brain atrophy, may be useful in early detection of Alzheimer's.

Several groups of researchers have compared CSF biomarkers and brain structure changes to see which most accurately predicts future cognitive decline in patients with MCI. Studies led by investigators at the Mayo Clinic, Rochester, MN, (Vemuri et al., 2010) and the University of Oslo (Fjell et al., 2010) found that structural changes predicted cognitive change more accurately than did CSF biomarker levels. Indeed, the Mayo study followed ADNI participants with either normal cognition, MCI, or Alzheimer's for 1 year and saw little change in CSF biomarker levels. However, MRI brain

scans indicated brain degeneration and cognitive decline in all participants. Many of the same Mayo Clinic investigators in a later study (Jack, Wiste, et al., 2010) found that measurements of brain amyloid (using CSF and brain imaging) and structural MRI were equally accurate in predicting cognitive decline in 218 ADNI participants diagnosed with MCI. However, when they looked at just the participants with significant levels of brain amyloid, structural changes more accurately predicted cognitive decline as opposed to amyloid levels.

At this stage, in a research setting, brain structural changes seem more reliable than CSF biomarkers in predicting cognitive decline. These observations also support the ideas that cognitive dysfunction is more closely associated with loss of brain tissue, especially with shrinkage of the hippocampus, than with amyloid or tau deposition, and that individuals vary in the rates at which they develop CSF abnormalities, changes in brain structure, and cognitive decline.

Additional references:

- Jack CR Jr. et al. (2010) Hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade. Mayo Clinic, Rochester, MN. Supported by NIA.
- Montine TJ et al. (2011) Tau protein and beta-amyloid(1-42) CSF levels in different phenotypes of Parkinson's disease. Palacky University, Olomouc, Czech Republic. Supported by NIEHS, NINDS, and NIA.

Imaging the Living Brain

Imaging enables researchers to study the structure and functioning of the brain. Tools include PET imaging using radioactive PiB, an agent that detects levels of beta-amyloid in the living brain, and MRI to measure brain volume. There is already evidence that structural and PiB imaging can identify early disease stages of Alzheimer's before symptoms of cognitive decline appear.

Scientists are also looking for ways to detect even earlier stages of the disease—before significant beta-amyloid deposition, cell loss, and brain atrophy, when treatment might be more effective in preventing disease progression. New research suggests that fMRI scanning, which measures changes in blood flow related to brain activity, may be able to capture such signs of Alzheimer's disease.

Two fMRI studies have identified early changes in the activity of the default-mode network (DMN), or brain regions engaged when a person is focused inward, such as when daydreaming, envisioning, or recalling the past. The first study, at Harvard University, Cambridge, MA, involved 75 older participants, ranging from people with normal cognition to those with mild Alzheimer's dementia, who performed a memory task while their brains were being scanned (O'Brien et al., 2010). The researchers then compared the fMRI patterns of APOEε4 carriers (those with a known genetic risk for late-onset Alzheimer's) and noncarriers. Even among cognitively normal subjects, carriers showed greater activity in a DMN-related part of the brain that is normally less active during memory tasks and is one of the earliest sites of beta-amyloid deposition. Loss of the ability to properly "quiet" this region may impair the formation of memories. The abnormal fMRI response pattern in this region may be an early indicator of Alzheimer's-related changes taking place in the brain and may help identify those at risk of developing the disease.

The second study, at Washington University School of Medicine, St. Louis, suggests that disruption of DMN function may occur independently of other markers, such as abnormal amounts of amyloid in the brain (Sheline, Raichle, et al., 2010). The researchers performed fMRI scans on 100 cognitively normal people (mean age 62) whose brains showed little or no evidence of beta-amyloid deposition on PiB scans. They found APOEε4 carriers showed significant disruption of the DMN compared to noncarriers. This disruption was also seen in 70 of the 100 participants who, besides being free of amyloid buildup in the brain, also had normal levels of the protein in their CSF. These findings suggest that

changes in the DMN may be a precursor rather than a consequence of beta-amyloid deposition and may help to identify those at risk.

Additional references:

- Chao LL et al. (2010) Evidence of neurodegeneration in brains of older adults who do not yet fulfill MCI criteria. San Francisco VA Medical Center. Supported by NIA.
- Chen K et al. (2010) Twelve-month metabolic declines in probable Alzheimer's disease and amnestic mild cognitive impairment assessed using an empirically pre-defined statistical region-of-interest: findings from the Alzheimer's Disease Neuroimaging Initiative. Banner Alzheimer's Institute and Banner Good Samaritan PET Center. Supported by NIA and NIMH.
- Pihlajamäki M et al. (2010) Evidence of altered posteromedial cortical FMRI activity in subjects at risk for Alzheimer disease. University of Kuopio, Kuopio, Finland. Supported by Academy of Finland, NINDS, and NIA.
- Yassa MA et al. (2010) Pattern separation deficits associated with increased hippocampal CA3 and dentate gyrus activity in nondemented older adults. University of California, Irvine. Supported by NIA.

Developing New Cognitive Tests

Dementia screening is not routine in medical practice and, as a result, the early stages of MCI and Alzheimer's dementia often are not detected. A primary reason for the lack of routine screening is that no single screening tool has been shown to detect cognitive impairment quickly and accurately in older adults. Among the benefits of screening is the opportunity to learn about therapeutic options, including clinical trials, as well as to understand and prepare for expected changes in the future, if dementia is diagnosed.

In one study, researchers examined a relatively new diagnostic tool, the AD8, to compare it to existing tools. They also wanted to see if the AD8 relates to the presence of biomarkers for Alzheimer's disease determined from analysis of cerebrospinal fluid or through brain imaging. The value of a highly accurate instrument is that it would spare patients from unnecessary diagnostic testing that may be invasive and/or expensive.

The AD8 consists of eight yes-or-no questions about everyday function. It can be given to the person being screened or to family members or others familiar with that person. In a Washington University, St. Louis, study, AD8 test scores of 257 older people correlated well with results of more extensive neuropsychological tests and Alzheimer's biomarkers from the same participants (Galvin et al., 2010). Researchers also found the AD8 test to be more sensitive than the Mini Mental State Exam, one of the most commonly used tests for Alzheimer's dementia. Researchers and clinicians continue to examine the AD8 and other ways to easily and quickly screen for Alzheimer's disease in a clinical setting.

As the new Alzheimer's disease diagnostic guidelines point out, early cognitive changes in Alzheimer's dementia may be evident in cognitive domains other than memory. One such domain is "executive function," which includes control of attention. The Stroop test measures a person's ability to stay focused on a task while being presented with distracting information (for example, to name the color of ink in which words are printed while ignoring the words themselves—a task that becomes harder if the word "red" is printed in blue ink). Washington University, St. Louis, researchers created a new version of the Stroop test that engages more of the brain's thinking capacity by asking a person to switch back and forth between two different tasks with two different sets of instructions (Hutchison et al., 2010). In a small study of 64 cognitively normal older adults and 32 adults with very mild Alzheimer's dementia, the new test version was particularly good at discriminating between people with Alzheimer's and those with normal cognition for their age.

Fluctuating Symptoms in Alzheimer's Disease

As caregivers often notice, people with Alzheimer's can have "good days" and "bad days." Fluctuations in cognition, attention, and alertness have long been recognized as a central feature of Lewy body dementia, but their occurrence in Alzheimer's has been less well studied. These fluctuations can also occur in people with normal cognition.

Researchers from Washington University School of Medicine, St. Louis, assessed the prevalence of cognitive fluctuations in 511 people, more than half of whom were cognitively normal and the remainder with varying severity of dementia (Escandon et al., 2010). Fluctuations were assessed via questionnaires filled out by their spouses or adult children.

The researchers found that 12 percent of the participants with Alzheimer's had spontaneous changes in cognition, including episodes of daytime drowsiness or lethargy (sleeping for more than 2 hours during the daytime), and episodes of illogical, disorganized thinking, or staring into space for long periods. People with three or four symptoms of cognitive fluctuation were eight times more likely to be diagnosed with dementia, and those with fluctuations were more likely to have a greater severity of dementia. Not surprisingly, they also performed more poorly on neuropsychological tests, particularly if their symptoms included disorganized or illogical thinking. This finding suggests that assessing patients for cognitive fluctuations could be an important factor for clinicians when evaluating and treating people with Alzheimer's.

Sensory Changes

People with Alzheimer's disease often experience problems with their sense of smell, even in the earliest stages of the disease. To root out why Alzheimer's might cause such problems, researchers at Northwestern University in Evanston, IL, performed fMRI scans of 10 participants with Alzheimer's and 10 who were cognitively normal (Li W et al., 2010). The people with normal cognition could correctly judge whether pairs of odors were more similar or different, but those with Alzheimer's could not. At the same time, fMRI scans showed the people with Alzheimer's had impaired functioning of the piriform cortex, a pear-shaped region of the brain that plays an important role in distinguishing odors. This study suggests that impaired function of the piriform cortex might help in diagnosing Alzheimer's.

In another study, New York University, New York City, researchers used a mouse model to probe how Alzheimer's affects the sense of smell (Wesson et al., 2010). They first measured how long the mice sniffed at scented cotton swabs after repeated presentations of the same odor. Normally, mice lose interest in odors they have already smelled, and the speed at which they do so is a measure of olfactory function. Alzheimer's disease model mice spent more time sniffing smells they had already encountered, while the normal mice spent more time investigating new smells. This difference continued as the mice aged, with the model mice much slower at detecting familiar smells.

Similar to people with Alzheimer's, the model mice also had difficulty discriminating between different odors. These deficits appeared as early as 3 months of age, as did very early signs of Alzheimer's pathology—deposits of beta-amyloid in various parts of brain important to the sense of smell. Because the earliest stages of beta-amyloid deposition appear to impact odor learning tasks in mice, researchers are continuing to study such odor learning tasks for their use in diagnosis and, ultimately, in testing of new therapies.

Motor Changes

Slowing of motor function—such as walking—is associated with greater risk of cognitive decline in older people and may precede the onset of cognitive impairment. Researchers at Oregon Health Sciences University in Portland analyzed the rate of motor decline over the course of 20 years in 204 older adults who were cognitively normal at the start of the study (Buracchio et al., 2010). Although a decline in gait speed is common in older adults, participants who eventually developed MCI showed faster rates of decline in both walking speed and finger-tapping speed than those who remained cognitively normal. In addition, motor function declined dramatically at distinct points among those who eventually developed MCI. For men, the sudden acceleration in gait-speed decline occurred about 14 years before the onset of MCI; for women, at 6 years. What causes this acceleration in gait-speed decline among those destined to develop MCI is unclear. Walking requires a complex interplay of sensory, cognitive, and motor functions, and these systems may be impacted early in the Alzheimer's disease process.

Additional reference:

- Wilkins CH et al. (2010). A brief clinical tool to assess physical function: the mini-physical performance test. Washington University School of Medicine. Supported by NIA.

7 Testing Therapies to Treat, Delay, or Prevent Alzheimer's Disease

Clinical trials are the only way to test whether a potential intervention for Alzheimer's disease is safe and effective in humans. During a clinical trial, the experimental treatment is compared to the standard treatment or a placebo (an inactive ingredient). During a Phase I trial, a research team gives the treatment to a small number of participants and examines its safety and action in the body. The main goals are to establish the highest dose of a new drug that people can tolerate and to define the dose at which harmful side effects may begin. If the treatment appears to be safe, it will go on to Phase II and Phase III clinical trials.

Phase II trials involve larger numbers of people. In these trials, the study team wants to know whether the treatment is safe and effective at changing the course of the disease. Phase II trials occasionally also involve the use of a placebo. Results from Phase II trials give researchers an indication of the effective dose to use in Phase III trials.

Phase III trials are large studies that compare an experimental treatment with a placebo or standard treatment to determine safety and efficacy (whether the treatment has the power to produce an effect). Phase III trials are complex, expensive studies involving hundreds or even thousands of volunteers and are often conducted over a long period of time.

The most compelling scientific evidence comes from clinical trials that are *randomized* (participants are randomly assigned to receive either the treatment or placebo), *double-blinded* (neither participant nor researchers know which treatment the participant receives), and *placebo-controlled* (an inactive substance is given to one group of participants, while the drug being tested is given to another group). Randomized, double-blind, placebo-controlled studies are considered the "gold standard" of clinical trials.

Within NIH, the NIA is the primary institute supporting and conducting clinical trials on Alzheimer's disease, MCI, and age-related cognitive decline. NIA funds a wide array of investigator-initiated clinical trials for Alzheimer's, MCI, and age-related cognitive decline. Some trials focus on treatments for Alzheimer's that may preserve cognitive function for as long as possible and alleviate behavioral or psychiatric problems. Others involve efforts to slow disease progression, such as delaying MCI's progression to Alzheimer's dementia, a type of research called secondary prevention. Still others focus on primary prevention, or helping cognitively healthy people reduce their risk of developing Alzheimer's disease in the future. (See Table 1, page 48).

View a brief video of the NIA's Dr. Laurie Ryan describing the NIA's clinical trials program.

NIA Programs Support Clinical Trials

The NIA supports an infrastructure and funding opportunities to develop and test new Alzheimer's treatments via two major clinical trial programs: the Alzheimer's Disease Cooperative Study (ADCS) and the Alzheimer's Disease Pilot Clinical Trials Initiative. The latter initiative supports a number of preliminary clinical evaluations of interventions for MCI, Alzheimer's, and age-related cognitive decline that might not otherwise be pursued by industry.

The ADCS, a large clinical trials consortium with sites throughout the United States and Canada, is a major research initiative investigating both the cognitive and behavioral symptoms of Alzheimer's disease. ADCS investigators are developing innovative clinical trial designs, tools, and interventions, including therapies that might not otherwise be developed by industry. (See page 61 for more about the ADCS.) The most recent round of ADCS studies, funded since 2006, explore a variety of promising areas:

- **Docosahexaenoic Acid (DHA).** This completed trial examined whether treatment with DHA, an omega-3 fatty acid found in fish, would slow cognitive decline in

The NIA currently supports more than **30** *active clinical trials testing a wide range of* **interventions** *to prevent, slow, or treat mild cognitive impairment and/or Alzheimer's disease.*

people with Alzheimer's. Observational studies associate high fish consumption with reduced risk of the disorder, and studies in Alzheimer's mouse models show that dietary DHA reduces brain levels of beta-amyloid, oxidative damage associated with beta-amyloid, and neurotoxicity. The primary results of this trial are described below.

- **Intravenous Immunoglobulin (IVIg).** A blood product administered intravenously, IVIg contains naturally occurring antibodies against beta-amyloid. Preliminary studies have shown it may improve cognition. In addition, IVIg increased levels of anti-beta-amyloid antibodies in plasma and promoted clearance of beta-amyloid from CSF in a Phase III clinical trial. This ongoing, double-blind, randomized controlled trial will demonstrate whether IVIg is effective in treating Alzhiemer's.
- **Home-based Assessment.** This ongoing study, conducted in people age 75 and older, is examining the development and use of home-based assessments in clinical trials, using interviews over the telephone and/or via computer. Cognition, daily functioning, mood, and other factors will be evaluated in each of these innovative assessment and data collection methods, and then compared against traditional in-person methods. The findings from this study will provide information on how home-based assessments might be used in prevention trials. Such methods could significantly reduce the cost and increase the feasibility of participation in long-term clinical trials.
- **Resveratrol.** This Phase II, double-blind, randomized controlled trial, scheduled to begin in early 2012, will evaluate the impact of resveratrol treatment on Alzheimer's biomarkers and clinical outcomes in people with mild to moderate Alzheimer's disease. Resveratrol is an antioxidant compound found in grapes and red wine. Observational studies have shown that moderate consumption of red wine is associated with a lower incidence of Alzheimer's disease, and animal studies have demonstrated resveratrol's neuroprotective properties.

NIA-Funded Clinical Trials

The NIA currently supports more than 30 active clinical trials, including pilot and large-scale trials, of a wide range of interventions to prevent, slow, or treat Alzheimer's disease and/or MCI (see Tables 1 and 2). Of the primary prevention trials, two are NIA-funded add-ons to large NIH trials that address other primary outcomes.

One of these add-ons is part of the National Heart, Lung, and Blood Institute's Systolic Blood Pressure Intervention Trial (SPRINT), which will evaluate the health effects of lowering systolic blood pressure from 140 to 120. The add-on study, funded by NIA and NINDS, called SPRINT-MIND, will assess the effect of lowering systolic blood pressure on cognitive decline and the development of MCI and Alzheimer's disease. The study will also use brain imaging to measure treatment effects on brain structure, including white matter lesions typical of vascular disease.

The second add-on study is Action to Control Cardiovascular Risk in Diabetes, a national study supported by the National Heart, Lung, and Blood Institute to examine the effect of different glucose-lowering strategies on the risk for cardiovascular disease. Based on previous studies linking diabetes with increased risk of cognitive decline and Alzheimer's disease, the trial's Memory in Diabetes substudy looked at cognitive function and brain volume in this population.

NIA-funded clinical trials are exploring the connection between Alzheimer's and various diseases, such as diabetes and cardiovascular disorders, as well as lifestyle factors that may influence disease onset and progress, such as exercise, stress, and hormones.

Reports from Recently Completed Clinical Trials

While no new Alzheimer's disease interventions were found effective and safe in 2010, the results of clinical trials reported during this period still provide important insights into the disease and will benefit future studies. For example, researchers found what may be important differences in treatment effects in people who do and do not carry the APOEε4 risk-factor gene for late-onset Alzheimer's. One private study involved bapineuzumab, an antibody that binds to beta amyloid. A 2009 report found different responses to treatment among APOEε4 carriers and noncarriers. A second finding, involving DHA, is described below. Results such as these are propelling further trials targeting select subgroups of Alzheimer's patients.

DHA

Epidemiological studies have suggested that consumption of DHA supplements or fish containing DHA may reduce risk of Alzheimer's disease. Additionally, Alzheimer mouse model studies have shown that DHA consumption reduces beta-amyloid pathology. In a clinical trial conducted by the NIA-supported Alzheimer's Disease Cooperative Study (ADCS), 402 participants with mild to moderate Alzheimer's were given daily supplements of either 2 grams of DHA or a placebo (Quinn et al., 2010). After 18 months of treatment, there were no significant differences in the rate of cognitive decline between the DHA-treated and control groups. However, DHA did appear to slow cognitive decline in those who did not carry the APOEε4 gene.

These results raise the possibility that DHA supplementation could be effective if started before the appearance of cognitive symptoms. Alternatively, because the disease may progress differently in APOEε4 carriers and non-carriers, treatments may need to be tailored according to genetic type.

Insulin Nasal Spray

In a pilot clinical trial conducted by the Veterans Affairs Puget Sound Health Care System in Seattle and Tacoma, WA, researchers tested whether restoring normal insulin function in the brain might provide cognitive benefit and slow the progression of Alzheimer's disease (Craft et al., 2011). More than 100 volunteers with MCI or mild to moderate Alzheimer's disease received insulin nasal spray or a placebo and had their memory, cognition, and functional ability measured before and after the 4-month treatment. Cerebrospinal fluid was analyzed and brain scans conducted before and after treatment.

The results showed that a nasal-spray form of insulin delayed memory loss and preserved general cognition and did not raise the insulin levels outside of the brain. These results point to the need for larger trials of insulin nasal-spray therapy to further test its effectiveness in treating Alzheimer's disease.

Cholesterol-Lowering Statins

Researchers have hypothesized that statins (cholesterol-lowering drugs), may be useful for treating Alzheimer's. Animal studies have shown that high-fat diets increased accumulation of amyloid in the brain and that statins reduced those levels. Some but not all epidemiological studies in humans have suggested that statins may decrease risk for Alzheimer's, and some small clinical trials supported the use of statins to benefit cognition.

However, an ADCS-supported, randomized, double-blind study of simvastatin did not show delayed progression of the disease (Sano, Bell, et al., 2011). Some 400 people with mild to moderate Alzheimer's disease participated in the 18-month trial. One half received the drug and the other half received a placebo. Cognitive testing of the participants did not show any benefits among those taking the statin.

Cholinesterase Inhibitors

Many people continue to drive after receiving a diagnosis of Alzheimer's. Because people diagnosed with mild to moderate Alzheimer's are usually treated with a cholinesterase inhibitor drug, researchers wondered how these drugs affect tasks related to driving performance. Researchers at Brown University in Providence, RI, studied attention and executive function in 24 participants newly diagnosed with Alzheimer's, testing their performance before and after 3 months of treatment with a cholinesterase inhibitor (Daiello et al., 2010). They found that participants performed significantly better after treatment on both a computer-simulated driving test and on visual attention tasks.

Additional references:

- Farlow MR et al. (2010) Effectiveness and tolerability of high-dose (23 mg/d) versus standard-dose (10 mg/d) donepezil in moderate to severe Alzheimer's disease: A 24-week, randomized, double-blind study. Indiana University School of Medicine. Supported by NIA.

- Wang L et al. (2010) Donepezil treatment and changes in hippocampal structure in very mild Alzheimer disease. Washington University School of Medicine. Supported by NIA and NIMH.
- Weintraub D et al. (2010) Sertraline for the treatment of depression in Alzheimer disease. University of Pennsylvania School of Medicine. Supported by NIMH.

Exercise

Epidemiological studies as well as some intervention studies have suggested that physical exercise may play a role in reducing risk for Alzheimer's disease (see *Exercise and Maintaining Cognitive Health,* page 30). Researchers at the University of Illinois, Urbana-Champaign have shown that exercise can stimulate the brain's ability to maintain and make new network connections that are vital to healthy cognition (Voss et al., 2010). In the year-long study, 65 older people exercised daily, doing either an aerobic exercise program of walking for 40 minutes or a nonaerobic program of stretching and toning exercises.

At the end of the trial, the walking group showed improved connectivity in the brain's default-mode network, or DMN. In fact, their DMN activity—which is the part of the brain engaged in daydreaming, envisioning the future, and recalling the past—closely resembled those of young adults. The walking group also improved on executive function tasks necessary to planning and carrying out specific behaviors, like figuring out what to have for dinner, and then going to the kitchen and selecting the appropriate ingredients. This study suggests that exercise could be explored to see whether it can even help reverse cognitive decline and if aerobic exercise allows the brain to function at a more youthful level.

Additional references:

- Rubright J et al (2010) A memory and organizational aid improves Alzheimer disease research consent capacity: results of a randomized, controlled trial. University of Delaware School of Education. Supported by NIA.
- Sano M et al. (2010) Pilot study to show the feasibility of a multicenter trial of home-based assessment of people over 75 years old. Mount Sinai School of Medicine. Supported by NIA.

Hormones and Cognitive Health in Postmenopausal Women

Hormones such as estrogen and progesterone have important effects on the brain, many of which are potentially relevant to cognitive aging and Alzheimer's disease. Over the years, research findings have led to a variety of seemingly conflicting reports—both positive and negative—as to whether menopausal hormone therapy can prevent cognitive decline in postmenopausal women.

Some animal and observational studies comparing women who chose to take estrogen with those who did not have shown that estrogen may benefit cognition. However, controlled clinical trials of menopausal hormone therapy in older women have generally failed to show similar beneficial effects. The Women's Health Initiative Memory Study (WHIMS) reported in 2003 that prolonged treatment with estrogen and progestin (substances with a progesterone-like effect) actually increased the risk of cognitive decline and dementia in postmenopausal women age 65 and older.

How to reconcile these conflicting data? One central issue may be timing. The women in the WHIMS trial started treatment a decade or more after menopause. In contrast, the majority of women in the observational studies that showed estrogen benefited cognition began treatment soon after menopause. This difference has led researchers to wonder if it may be advantageous to begin treatment closer to menopause.

Support for that idea comes from a University of Pittsburgh study, in which women who began estrogen in the first year after menopause had the largest hippocampal volume (Erickson, Voss, et al., 2010). Two NIA-funded clinical trials are currently studying the timing of menopausal hormone therapy on cognition and other health factors: the Kronos Early Estrogen Prevention Study-Cognition and Affective Study (KEEPS-CA) and the Early Versus Late Intervention Trial with Estrogen (ELITE).

Response to estrogen may also depend on whether the transition to menopause occurs naturally over a number of years or is the result of surgery, such as a hysterectomy to remove the uterus. Researchers at Arizona State University found that estrogen had different effects on cognition in animal models that allow such a comparison. Estrogen impaired memory-test performance in rats transitioning naturally into menopause, but it improved performance in surgically menopausal rats. The reason for this difference is unknown (Acosta et al., 2010).

Today, most women who receive menopausal hormone therapy use estrogen in a variety of forms and doses and often in combination with progesterone or a progestin such as medroxyprogesterone acetate (MPA). Animal studies point to progestins, particularly MPA, as possibly having a negative impact on cognition. A University of Illinois study of aged, surgically menopausal rats treated with estrogen and MPA showed the animals performed less well on memory tests than rats treated with estrogen alone or with estrogen and progesterone (Lowry et al., 2010). In a study of aged, surgically menopausal rats at Arizona State University, animals treated with high-dose MPA showed impaired memory performance compared to untreated rats (Braden et al. 2010).

Additionally, it appears that progesterone and progestins differ in their impact on brain health. University of Southern California researchers compared the effects of four clinically prescribed progestins on hippocampal cell growth and survival in adult female rats (Liu et al., 2010). When administered in combination with estrogen, two of the progestins appeared to have largely beneficial effects on hippocampal cell health. In contrast, a different set of progestins had mixed effects; they supported cell proliferation but simultaneously increased cell death. Because progestins are used in fertility therapy and for contraception as well as menopausal hormone therapy, their potentially varying effects on cognitive health warrants further investigation.

Additional references:

- Janicki SC, Schupf N. (2010) Hormonal influences on cognition and risk for Alzheimer's disease. Columbia University Medical Center. Supported by NIMH, NIA, NICHD, and NCI.
- Zhao Z et al. (2010) Epigenetic alterations regulate estradiol-induced enhancement of memory consolidation. Yale University. Supported by NIA.

TABLE 1. Ongoing Alzheimer's Disease/Mild Cognitive Impairment Prevention Trials Funded by NIA

TRIAL NAME	PRINCIPAL INVESTIGATOR/ INSTITUTION	INTERVENTION	POPULATION	TYPE OF TRIAL	ANTICIPATED COMPLETION DATE
		Nutritional			
AREDS2 (Age-Related Eye Disease Study 2)*	John Paul San Giovanni (Study Director), NEI	Macular xanthophylls (lutein and zeaxanthin) and/or omega-3 fatty acids (DHA and EPA)	People age 50-85 with age-related macular degeneration (AMD) in both eyes or advanced AMD in one eye	Primary Prevention	2015
PREADVISE (Prevention of Alzheimer's Disease by Vitamin E and Selenium)†	Frederick Schmitt, University of Kentucky	Vitamin E, selenium, vitamin E + selenium	Men age 60-90	Primary Prevention	2014
Vitamin E in Aging Persons with Down Syndrome	Arthur Dalton, Institute for Basic Research in Developmental Disability	Vitamin E	People age 50+ with Down syndrome, at high risk of developing Alzheimer's disease	Primary Prevention	2012
		Hormones			
ELITE (Early Versus Late Intervention with Estradiol)	Howard Hodis, University of Southern California	17β-estradiol	Healthy early (less than 6 years) or late (10 years +) menopausal women	Primary Prevention	2014
SMART (Somatotrophics, Memory, and Aging Research Trial)	Michael Vitiello, University of Washington	Growth hormone releasing hormone (GHRH)	People with mild cognitive impairment and healthy older adults age 55-80	Secondary Prevention	2011
Testosterone Supplementation in Men with MCI	Monique Cherrier, University of Washington	Testosterone	Older men with MCI and low testosterone	Secondary Prevention	2011
		Cardiovascular			
ASPREE (Aspirin in Reducing Events in the Elderly)	Richard Grimm, Berman Center for Outcomes and Clinical Research; John McNeil, Monash University	Aspirin	Healthy adults age 70+	Primary Prevention	2017

TABLE 1 continued

TRIAL NAME	PRINCIPAL INVESTIGATOR/ INSTITUTION	INTERVENTION	POPULATION	TYPE OF TRIAL	ANTICIPATED COMPLETION DATE
			Cardiovascular (Continued)		
SPRINT-MIND (Systolic Blood Pressure Intervention Trial-MIND)†	David Reboussin, Wake Forest University	Blood pressure lowering to <140 mmHg versus <120 mmHg	Adults age 55+ with systolic blood pressure of 130 mmHg or higher, history of cardio-vascular disease, high risk for heart disease	Primary Prevention	2017
			Metabolic		
Metformin in Amnestic Mild Cognitive Impairment	Jose Luchsinger, Columbia University	Metformin	Overweight/obese older adults with mild cognitive impairment	Secondary Prevention	2012
Pioglitazone and Exercise Effects on Older Adults with Mild Cognitive Impairment and Metabolic Syndrome	Robert Schwartz, University of Colorado, Denver	Pioglitazone	Overweight/obese older adults with mild cognitive impairment	Secondary Prevention	2012
			Nonpharmacological		
Exercise Versus Cognitive Interventions for Elders at Risk for Dementia	David Loewenstein, University of Miami	Cognitive training, aerobic exercise training, cognitive training + aerobic exercise training	People with mild cognitive impairment	Secondary Prevention	2012
Memory Training Intervention in Mild Cognitive Impairment	Miriam Mintzer, Johns Hopkins University	Repetition lag training procedure (RLTP)	People with mild cognitive impairment	Secondary Prevention	2014
Preventing Cognitive Decline in African Americans with Mild Cognitive Impairment	Barry Rovner, Thomas Jefferson University	Home-based behavioral treatment	African Americans with mild cognitive impairment	Secondary Prevention	2016

Note: For information on new and currently recruiting trials, visit: *www.nia.nih.gov/alzheimers* or *ClinicalTrials.gov*.

* Co-funded primary prevention trial: AREDS2 (led by National Eye Institute).

† NIA-funded primary prevention add-on trials: PREADVISE (add-on to National Cancer Institute's SELECT trial); SPRINT-MIND (add-on to National Heart, Lung, and Blood Institute's and National Institute of Diabetes and Digestive and Kidney Diseases' SPRINT trial; co-funded with the National Institute of Neurological Disorders and Stroke).

TABLE 2. Ongoing Alzheimer's Disease/ Mild Cognitive Impairment Treatment and Feasibility Clinical Trials Funded by NIA

TRIAL NAME	PRINCIPAL INVESTIGATOR/ INSTITUTION	INTERVENTION	POPULATION	ANTICIPATED COMPLETION DATE
Treatment Trials—Cognition				
Nutritional				
Lipoic Acid and Omega-3 Fatty Acids in Alzheimer's Disease	Lynne Shinto, Oregon Health & Science University	Lipoic acid and/or omega-3 fatty acids (DHA and EPA)	People with Alzheimer's disease	2014
Hormones				
Raloxifene for Women with Alzheimer's Disease	Victor Henderson, Stanford University	Raloxifene (selective estrogen receptor modulator or SERM)	Older women with Alzheimer's disease	2012
Nonpharmacological				
ADMIT (Alzheimer's Disease Multiple Intervention Trial)	Chris Callahan, Indiana University	Home-based occupational therapy	People with Alzheimer's disease	2016
Aerobic Fitness in Slowing the Progression of Alzheimer's Disease	Jeffrey Burns, University of Kansas	Aerobic exercise training	People with Alzheimer's disease	2014
Therapeutic Effects of Cataract Removal in Alzheimer's Disease	Grover Gilmore, Case Western Reserve University	Cataract removal	Adults 65 and older with both Alzheimer's disease and cataracts	2014
Other Interventions				
AAV-NGF Gene Delivery in Alzheimer's Disease	Paul Aisen, University of California, San Diego	Nerve growth factor (NGF) gene delivery	People with Alzheimer's disease	2014
Intravenous Immunoglobulin (IVIg) for Treatment of Alzheimer's Disease (passive immunization)*	Norman Relkin, Weill Medical College of Cornell University	IVIg	People with Alzheimer's disease	2013
Treatment Trials—Neuropsychiatric Comorbidities				
ADMET (Apathy in Alzheimer's Disease Methylphenidate Trial)	Jacobo Mintzer, Medical University of South Carolina; Krista Lanctot; University of Toronto; Paul Rosenberg, Johns Hopkins University	Methylphenidate	People with Alzheimer's disease	2012
Antipsychotic Discontinuation in Alzheimer's Disease	Davangere Devanand, NYSPI/Columbia University	Risperidone	People with Alzheimer's disease	2011

TABLE 2 continued

TRIAL NAME	PRINCIPAL INVESTIGATOR/ INSTITUTION	INTERVENTION	POPULATION	ANTICIPATED COMPLETION DATE
Treatment Trials—Neuropsychiatric Comorbidities (Continued)				
CITAD (Citalopram Treatment for Agitation in Alzheimer Dementia)	Constantine Lyketsos, Johns Hopkins University	Citalopram	People with Alzheimer's disease	2014
Pilot Combination Treatment Trial of Mild Cognitive Impairment with Depression	Davangere Devanand, New York State Psychiatric Institute/ Columbia University	Citalopram and donepezil	People with mild cognitive impairment	2015
Prazosin Treatment for Disruptive Agitation in Alzheimer's Disease	Elaine Peskind, University of Washington	Prazosin	People with Alzheimer's disease	2013
TREA (Treatment Routes for Exploring Agitation)	Jiska Cohen-Mansfield, Hebrew Home of Greater Washington	TREA–systematic approach to individualizing nonpharmacological interventions for persons with dementia	Nursing home residents with Alzheimer's disease	2012
Proof of Concept Trials				
Cardiovascular				
Effects of Simvastatin on CSF Alzheimer's Disease Biomarkers in Cognitively Normal Subjects	Gail Li, University of Washington	Simvastatin	Cognitively normal adults age 45-64	2013
Pilot Trial of Carvedilol in Alzheimer's Disease	Giulio Maria Pasinetti, Mt. Sinai School of Medicine; Paul Rosenberg, Johns Hopkins University	Carvedilol	People with Alzheimer's disease	2015
Statin Effects on Beta-Amyloid and Cerebral Perfusion in Adults at Risk for Alzheimer's Disease	Cynthia Carlsson, University of Wisconsin, Madison	Simvastatin	Adults age 45-65 at high risk of Alzheimer's disease (family history, APOE4)	2013
Hormones				
Estrogen Receptor-beta phytoSERMs for Management	Lon Schneider, University of Southern California	ER2-selective phytoestrogens (phytoSERMs—selective estrogen receptor modulators)	Postmenopausal women age 50-59	2014
Metabolic				
Glucose Regulation and Memory in Alzheimer's Disease	Suzanne Craft, University of Washington	Improved insulin resistance, 3 studies: diet, triglyceride emulsion, rosiglitazone	People with Alzheimer's disease and age-matched healthy older adults	2016

TABLE 2 continued

TRIAL NAME	PRINCIPAL INVESTIGATOR/ INSTITUTION	INTERVENTION	POPULATION	ANTICIPATED COMPLETION DATE
		Nonpharmacological		
Conversational Engagement As a Means to Delay Alzheimer's Disease Onset	Hiroko Dodge, Oregon Health & Science University	Internet-based conversational engagement	Adults age 75+	2014
Effects of Standardized Aerobic Exercise Training on Neurocognition and Neurodegeneration	Thomas Obisesan, Howard University	Aerobic exercise training	African Americans with Alzheimer's disease	2012
Exercise and Health Promotion for Mild Cognitive Impairment	Linda Teri, University of Washington	Two exercise programs (one for individuals with mild cognitive impairment and the other for cognitively intact older adults)	People with mild cognitive impairment	2012
Lifestyle Interventions and Independence for Elders (LIFE)	Marco Pahor, University of Florida	Aerobic exercise, resistance, and flexibility exercises	Sedentary adults age 70-89	2015
Mild Cognitive Impairment: Cerebrovascular Dysfunction and Exercise Training	Rong Zhang and Hanzhang Lu, University of Texas Southwestern	Endurance exercise training	People with mild cognitive impairment	2014
Neural Effects of Exercise, Cognitive, or Combined Training in Alzheimer's Disease At-Risk Elders	Stephen Rao, Cleveland Clinic	Cognitive training, aerobic exercise training, cognitive training + aerobic exercise training	Healthy adults age 65-85	2012
		Other Interventions		
fMRI Activation in Mild Cognitive Impairment	Michela Gallagher, Johns Hopkins University	Levetiracetam	People with mild cognitive impairment	2012
Thalidomide As BACE1 Inhibitor in Alzheimer's Disease	Yong Shen, Roskamp Insititute; Marwan Sabbagh, Banner Sun Health Research Institute	Thalidomide	People with Alzheimer's disease	2012

Note: For information on new and currently recruiting trials, visit: *www.nia.nih.gov/alzheimers* or *ClinicalTrials.gov*.

*Alzheimer's Disease Cooperative Study trial.

TABLE 3. Ongoing Age-Related Cognitive Decline Clinical Trials Funded by NIA

TRIAL NAME	PRINCIPAL INVESTIGATOR/ INSTITUTION	INTERVENTION	POPULATION	ANTICIPATED COMPLETION DATE
		Cognitive Training		
Active Interventions for the Aging Mind	Denise Park, University of Texas, Dallas	Cognitive enrichment through training in digital photography or quilting	Healthy adults age 60+	2012
Brain-Based Approach to Enhancing Executive Control Functions in Healthy Aging	Mark D'Esposito, University of California, Berkeley	Cognitive training	Healthy adults age 50+	2012
Expanding the Implementation of an Effective Cognitive Aging Intervention	Helga Noice, Elmhurst College	Cognitive enrichment	Healthy adults age 65+	2010
Experience Corps Trial: Improving Health in Older Populations through Generativity	George Rebok, Johns Hopkins University	Health promotion for older adults embedded within a social engagement program (volunteering in schools)	Healthy adults age 60+	2011
Senior Odyssey: A Test of the Engagement Hypothesis of Cognitive Aging	Elizabeth Stine-Morrow, University of Illinois, Urbana-Champaign	Cognitive enhancement through participation in the Odyssey of the Mind program	Healthy adults age 60+	2012
Speed of Processing Modes to Prevent Cognitive Decline in Older Adults	Fredric Wolinsky, University of Iowa	Comparison of standard versus enhanced visual processing training	Healthy adults age 50+	2011
		Omega-3 Fatty Acids and Antioxidants		
Omega-3 and Blueberry Supplementation in Age-Related Cognitive Decline	Robert Krikorian, University of Cincinnati	Omega-3 and blueberry supplements	Healthy adults age 62-80	2012
		Cardiovascular		
Aging and the Renin-Angiotensin System in Elderly Hypertensive Individuals	Ihab Hajjar, University of Southern California	Angiotensin receptor blocker, angiotensin-converting enzyme inhibitor, diuretic	Adults age 60+ with uncontrolled hypertension and cognitive impairment	2012
		Hormones		
Estrogen Effects on Cholinergic Function in Older Women	Paul Newhouse, Vanderbilt University	Acute or chronic 17β-estradiol + muscarinic and nicotinic cholinergic antagonist	Healthy women age 50+	2014

TABLE 3 continued

TRIAL NAME	PRINCIPAL INVESTIGATOR/ INSTITUTION	INTERVENTION	POPULATION	ANTICIPATED COMPLETION DATE
		Hormones (Continued)		
Estrogen Use in Protection from Cognitive Decline	Natalie Rasgon, Stanford University	Continuation of or removal from post-menopausal estrogen treatment	Healthy women age 50-65	2011
Hormones and Cognitive Processing in Early Postmenopausal Women	Yolanda Smith, University of Michigan	Estradiol and prometrium (progesterone)	Healthy early post-menopausal women age 45-55	2011
KEEPS-CA (Kronos Early Estrogen Prevention Study–Cognitive and Affective Study)	Sanjay Asthana, University of Wisconsin, Madison	Oral conjugated equine estrogen and transdermal 17β-estradiol	Healthy postmenopausal women age 42-58	2012
Sex Steroids and Cognition in Postmenopausal Women	Elliot Hirshman, University of Maryland, Baltimore County	Dehydroepiandrosterone (DHEA)	Healthy postmenopausal women age 55-65 and 70-80	2011
Testosterone Trial	Peter Snyder, University of Pennsylvania	Testosterone gel	Older men	2015
		Exercise		
Cognitive Benefits of Aerobic Exercise Across the Lifespan	Yaakov Stern and Richard Sloan, Columbia University	Stretching/toning or aerobic conditioning	Healthy adults age 25-65	2015
Dose-Response Study of Exercise in Older Adults	Jeffrey Burns, University of Kansas	Aerobic exercise	Healthy older adults	2012
Exercise, Age-Related Memory Decline, and Hippocampal Function	Scott Small and Richard Sloan, Columbia University	Exercise training or maintenance of sedentary lifestyle	Healthy adults age 20-65	2015
		Exercise and Cognitive Training		
Brain and Cognitive Changes after Reasoning or Physical Training in Cognitively Normal Seniors	Sandra Chapman, University of Texas, Dallas	Cognitive training, aerobic exercise	Adults age 60-75	2011
Combined Exercise and Cognitive Training Intervention in Normal Aging	Yaakov Stern, Columbia University	Aerobic exercise and cognitive training	Healthy adults age 65-75	2012
Combining Exercise and Cognitive Training to Improve Everyday Function	Ellen Binder and Mark McDaniel, Washington University	Aerobic exercise and cognitive training	Healthy adults age 55-75	2012

TABLE 3 continued

TRIAL NAME	PRINCIPAL INVESTIGATOR/ INSTITUTION	INTERVENTION	POPULATION	ANTICIPATED COMPLETION DATE
Exercise and Cognitive Training (Continued)				
Impact of Exercise and Engagement on Cognition in Older Adults	Denise Park, University of Texas, Dallas	Walking, exercise regimen (aerobic tasks); quilting, photography (cognitive tasks)	Healthy adults age 60-85	2011
Improvement of Visual Processing in Older Adults	Karlene Ball, University of Alabama, Birmingham	Combination of visual processing training and exercise	Healthy adults age 65+	2011
Influence of Fitness and Cognitive Training on Brain and Cognition	Arthur Kramer, University of Illinois, Urbana-Champaign	Aerobic training (walking), combined aerobic training/cognitive training (dancing)	Adults age 60-75	2015
Tai Chi and Guided Autobiography for Remediation of Age-Related Cognitive Decline	Victor Henderson, Stanford University	Low-impact Tai Chi exercise and autobiographical writing	Healthy adults age 70+	2012
Other				
Guanfacine Treatment for Prefrontal Cognitive Dysfunction in Elderly Subjects	Christopher Van Dyck, Yale University	Guanfacine	Healthy adults age 75+	2011
Mechanisms of Cognitive Impairment in Chronic Kidney Disease	Manjula Kurella Tamura, Stanford University	Frequent hemodialysis	Adults age 55+	2012

Note: For information on new and currently recruiting trials, visit: *www.nia.nih.gov/alzheimers* or *ClinicalTrials.gov*.

8 Advancing Support for Caregivers

As the search for more effective interventions continues, people with Alzheimer's and their caregivers can turn to strategies that may improve their quality of life. These strategies include seemingly simple but important approaches, such as providing clear and informative information, learning about changes to expect as the disease progresses, and having resources to help prepare for these changes.

More intensive, formalized treatment programs aimed at improving patient care and reducing stress for caregivers are also being developed and tested. Some of these programs use occupational therapy-based strategies to improve the lives of people with Alzheimer's and to teach their caregivers skills to protect their own health and cope with the intense demands of caregiving. Several of these nonpharmacological interventions have been tested in controlled clinical trials and found to significantly improve the well-being of people of people with Alzheimer's and their caregivers.

Factors in Caregiving and Mortality

Caring for people with dementia is challenging, but support for caregivers can help ease the burden and may result in better outcomes for Alzheimer's patients. A University of Pittsburgh team looked at which factors predicted how care was provided—at home or elsewhere, by family or others—to 950 people with Alzheimer's who were residing at home when the study began (Schulz et al., 2010). Over the course of 18 months, people whose caregivers reported increasing difficulty in coping with the person's memory problems were more likely to be placed in care facilities, as were people who were Caucasian as opposed to African American or Hispanic. Importantly, people whose caregivers received the Resources for Enhancing Alzheimer's Caregiver Health (REACH) intervention were also found to be at reduced risk of death. Understanding factors that influence care transitions and mortality in dementia is important both to those with the disorder and their caregivers and physicians, so that everyone involved can plan for the future.

Reducing Caregiver Stress

Surveys suggest that more than 70 percent of people diagnosed with Alzheimer's disease live at home, where family and friends provide nearly most of their care. The amount of time caregivers spend taking care of their loved ones ranges from 69 to 117 hours per week (Elliott et al., 2010). Not surprisingly, the burden and stress of these demands can wear on the physical and emotional health of caregivers. Finding effective strategies to alleviate their burden would benefit not only caregivers but also those with Alzheimer's.

Researchers at Yale University, New Haven, CT, investigated which patient symptoms caused the most burden and emotional distress for caregivers (Mohamed et al., 2010). They studied 421 people diagnosed with or suspected of having Alzheimer's who lived at home and required a significant amount of care that might otherwise place them in a care facility. Some of the clinical trial participants received medications intended to reduce Alzheimer's-related psychosis, agitation, and aggressive behaviors, while others received placebos.

Consistent with other studies, the researchers found it was not declines in their loved one's cognition or memory that affected caregivers most. Rather, caregivers' feelings of depression and stress depended on the severity of the patients' psychiatric and behavioral symptoms and declines in the patients' quality of life. Notably, those caring for their spouses reported more feelings of distress than did other caregivers. This result suggests that two effective steps toward alleviating caregiver burden might be targeting problem behaviors with both drug and other interventions and enhancing the quality of life of the person with Alzheimer's.

Receiving a dementia diagnosis is a life-altering event, and people often need education and psychosocial support to better cope with the news. Chapters of the Alzheimer's Association and the Alzheimer's Foundation of America and other community-based organizations offer group education and support programs for those with the disease and their caregivers. These programs enable people to share their experiences and concerns, learn more about their disease, reduce feelings of isolation, and get help coping with lifestyle changes and long-term care planning.

University of Washington researchers looked at the effectiveness of support in a controlled clinical trial of 142 pairs of participants, comprised of a person diagnosed

with early-stage dementia and his or her caregiver. The pairs were split into two groups: 96 received program support while 46 controls were put on a program waiting list (Logsdon et al., 2010). Compared to the control group, the Alzheimer's patients who received program support had reduced depression and behavioral problems, improved family communication, and a greater sense of self-efficacy. The improvements were modest, but were more pronounced for those who were more distressed after their diagnosis. Caregivers who attended the support groups did not report significant changes in their own quality of life, perhaps because the support program focused primarily on the needs of the person diagnosed with early-stage disease.

REACH-ing Out to Caregivers

Since 1995, the NIA and the National Institute of Nursing Research have funded two phases of a clinical trial to develop and test strategies for helping dementia caregivers manage their stress and emotional burden. The results of phases I and II of REACH (Resources for Enhancing Alzheimer's Caregiver Health) clinical trials are now being put into practice through two Federal agencies, the Veterans Administration and the Administration on Aging. The interventions include education on dementia, training in specific caregiving skills, and encouragement and techniques for emotional and physical self-care.

Nearly 500 caregivers participating in REACH II received either the intervention (nine in-home visits and three telephone contacts from REACH staff providing instruction and support in caregiving skills, stress management, and self-care) or no intervention. In 2010, researchers at the University of Alabama examined the self-reported health status of participants at the start of the study compared to its end (Elliott et al., 2010). The intervention also provided caregivers tools and resources to track and maintain their own health, and researchers were interested in the effectiveness of these tools. Caregivers who received the intervention reported better physical and emotional health and quality of sleep than those who did not.

Behavioral problems common in people with Alzheimer's—repeating statements over and over, waking others at night, refusing care or being combative—can cause considerable distress and depression for caregivers. However, caregivers are reluctant to discuss these problems with physicians, a University of Pittsburgh study found (Hunsaker et al., 2010). In a small study of 25 caregivers, 80 percent cited dementia-related problem behaviors in a questionnaire, but only 23 percent of them discussed those behaviors during medical visits. Caregivers were much more forthcoming with reports of patient memory problems, bringing them up almost 70 percent of the time they met with doctors.

Reporting problem behaviors requires the caregiver to raise a potentially sensitive topic, often while the person being discussed is in the room. The researchers noted that caregivers may be reluctant to discuss the behaviors, even when the doctor is the first to broach the topic. Caregivers who experienced more serious or frequent problem behaviors were more likely to discuss them, however. The study suggests exploring ways to encourage caregivers to be more assertive in discussing behavioral problems with clinicians, since these symptoms are some of the most stressful aspects of caregiving and, in many cases, can be treated.

Support for Patient/Caregiver Pairs

Thomas Jefferson University in Philadelphia developed the Care of Persons with Dementia in their Environments (COPE) program to support the physical function and quality of life for people with dementia and their caregivers. In the program, occupational therapists worked with caregivers during as many as 10 sessions over 4 months to identify patient routines, habits and interests, and caregiver concerns. The therapists also tested the cognition and functioning of the care recipient to identify strengths and deficits. The therapists then trained caregivers in home safety, to simplify tasks, and to reduce stress.

In a clinical trial, Jefferson researchers tested the COPE intervention in a group of 102 pairs of caregivers and their loved ones (Gitlin et al., 2010a). Compared to those who did not receive the intervention, the COPE participants with dementia were significantly less dependent on caregivers in carrying out activities of daily living and showed greater engagement in and enjoyment in activities. Caregivers with COPE had significantly improved well-being and confidence in their caregiving skills.

The same team from Thomas Jefferson University, Philadelphia, also looked at how a nondrug intervention aimed at helping family caregivers manage distressing behaviors in loved ones with dementia might improve patient and caregiver outcomes (Gitlin et al., 2010b). The program, called Advancing Caregiver Training or ACT, focused on problems arising from three sources: the patient (unmet needs, discomfort or pain, undiagnosed medical conditions); the caregiver (stress, communication style); and the environment (clutter, other hazards). The 24-week program included up to 11 home visits and telephone calls by health professionals, who identified potential triggers of patient behaviors. Caregivers received training and support in strategies to modify those triggers and reduce their own stress levels. Blood and urine samples found undiagnosed medical conditions in 34 percent of the patients.

Caring for people with **dementia** *is challenging, but support for caregivers can help ease the burden and may result in better* **outcomes** *for Alzheimer's patients.*

Compared to control caregivers, those who received the ACT intervention reported significant improvements in difficult patient behaviors, reduced upset and enhanced confidence in managing the behaviors, less negative communication, less burden, and improved well-being. In this study, the overwhelming majority of caregivers identified behaviors typically not responsive to medications as being the most troublesome, highlighting the importance of nondrug interventions for these problems.

Additional references:

- McCurry SM et al. (2010) Predictors of short- and long-term adherence to a daily walking program in persons with Alzheimer's disease. University of Washington, Seattle. Supported by NIMH.
- Williams VP et al. (2010) Video-based coping skills to reduce health risk and improve psychological and physical well-being in Alzheimer's disease family caregivers. Duke University Medical Center. Supported by NIA.

9 Examining Social and Economic Risk Factors

Research suggests that certain racial, ethnic, and socioeconomic groups may be at greater risk for cognitive decline and dementia. Scientists are exploring ways to better define and overcome these differences, in part by broadening the diversity of people participating in research aimed at finding interventions.

For example, lower levels of education are tied to lower levels of cognitive function throughout adulthood and a higher risk for dementia. Researchers at Brandeis University, Waltham, MA, were interested in examining whether this association might be counteracted by activities that engage the mind and intellect. They surveyed 3,343 people between ages 32 and 84 and asked how often they engaged in four categories of cognitive activities: reading books, magazines, or newspapers; doing crosswords, puzzles, Scrabble™, or other word games; attending educational lectures or courses; and writing, such as letters, journal entries, or stories (Lachman et al., 2010).

The researchers administered memory tests to the participants and compared their answers about activities with performance on the tests. Participants with fewer than 4 years of college generally performed more poorly on memory tests than those with more education. However, those with less education who frequently engaged in cognitive activity had relatively better memory performance. In fact, less educated people who engaged in frequent cognitive activity had memory performance comparable to that of people with 4-year college degrees or higher. More research would be needed to test whether encouraging more frequent engagement in cognitive activities can reduce risk of cognitive decline in less advantaged populations.

The prevalence of Alzheimer's and other age-related cognitive disorders in America among African Americans and Hispanics equals or exceeds that among Caucasians. However, participation of these ethnic groups in biomedical research studies falls far below their representation in the general population. The most commonly reported barrier to recruiting ethnic minorities for research studies is a historical mistrust of researchers and the medical system.

Two NIA-funded Alzheimer's Disease Centers focused on that issue and reported an increase in their minority recruitment efforts. The University of California, Davis, Alzheimer's Disease Center developed an outreach program that included educational presentations at community churches, senior centers, and support groups. The program also encouraged word-of-mouth referrals from study participants (Hinton et al., 2010). The Bryan Alzheimer's Disease Research Center at Duke University, Durham, NC, emphasized partnerships between community members and researchers to identify problem issues, recruit participants, and share research findings with the community, with transparency and accountability of the research investigators being a key goal (Ballard et al., 2010). Researchers hope that efforts such as these will lead to greater representation in research by these groups, so that interventions can be more effectively developed and tested to benefit everyone with cognitive decline and dementia.

Additional reference:

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beta memory imaging clinical risk alpha biomarkers

Advancing the Future of Alzheimer's Research:

NIA Research Infrastructure and Initiatives

It is critical that the Federal research program for Alzheimer's disease create and sustain an infrastructure that supports and enhances the scientific enterprise. The NIA's coordinating mechanisms and key initiatives are critical to this effort. By pooling and sharing data widely and efficiently using a well-established Alzheimer's disease research infrastructure, science is advancing even within the limits of constrained resources.

As the lead institute at NIH on Alzheimer's disease, the NIA is looking to the future in several ways:

- convening and collaborating in workshops in new scientific areas
- working across the NIH to vigorously discuss new science and opportunities for new investment
- partnering with other Federal agencies, not-for-profit groups, and industry in the shared goal of improved treatments, new prevention strategies, and better programs for caregivers and patients.

Infrastructure support includes:

NIA Intramural Research Program (IRP). In addition to funding a broad portfolio of aging-related and Alzheimer's research at institutions across the country, the NIA supports its own laboratory and clinical research program, based in Baltimore and Bethesda, MD. The NIA IRP focuses on understanding age-related changes in physiology and behavior, the ability to adapt to biological and environmental stresses, and the pathophysiology of age-related diseases such as Alzheimer's. Laboratory research ranges from studies in basic biology, such as neurogenetics and cellular and molecular neurosciences, to examinations of personality and cognition. The IRP also conducts clinical trials to test possible new

interventions for cognitive decline and Alzheimer's disease. The IRP leads the Baltimore Longitudinal Study of Aging, America's longest-running scientific study of human aging, begun in 1958, which has provided valuable insights into cognitive change with age.

Alzheimer's Disease Centers (ADCs). The NIA's ADCs form the backbone of the national Alzheimer's disease research effort. These multidisciplinary centers, located at 29 institutions nationwide, promote research, training and education, and technology transfer. With participation by the community, the Centers conduct longitudinal multicenter and collaborative studies of Alzheimer's disease diagnosis and treatment, age-related neurodegenerative diseases, and predictors of future change in people without dementia that may indicate the initial stages of development of the disease. The ADCs also conduct complementary studies, such as imaging studies and autopsy evaluations. All participants enrolled in the Centers receive a standard annual evaluation. Data from these evaluations are collected and stored by the National Alzheimer's Coordinating Center (NACC, see below) as the Uniform Data Set. The ADCs serve as sites for a number of major studies, such as national initiatives in clinical trials and imaging and biomarker research (see descriptions of ADCS and ADNI below).

National Alzheimer's Coordinating Center (NACC). The NIA established NACC in 1999 with the goal of pooling and sharing data on participants in Alzheimer Disease Centers studies. By 2005, NACC had collected data from some 77,000 ADC study participants, including neuropathic data from 10,000 brain autopsies. The NACC then added clinical evaluations and annual follow-ups to its protocol, enriching the database with detailed longitudinal data from 24,000 participants and 1,600 brain autopsies. The data are available to Alzheimer's researchers worldwide.

The NACC data are helping to reveal different symptom patterns in different subsets of Alzheimer's patients, patterns that would not have become apparent without analyzing a dataset of this size. The NACC also helps coordinate other NIA efforts, such as the identification and selection of appropriate postmortem material collected at ADCs to send to the National Cell Repository for Alzheimer's Disease for use in GWAS conducted by the ADGC.

In 2010, NACC data proved vital to research conducted on hippocampal sclerosis, an age-related condition often confused with Alzheimer's. Researchers used data from participants enrolled at ADCs and other major studies to take the first step—clinical differentiation comparing the features of hippocampal sclerosis with pure Alzheimer's disease (Nelson et al., 2010). The study involved the largest series of autopsy-verified patients with hippocampal sclerosis ever assembled and could only be done with coordination and funding by the NACC.

Alzheimer's Disease Cooperative Study (ADCS). The NIA launched the ADCS in 1991 to develop and test new interventions and treatments for Alzheimer's disease that might not otherwise be developed by industry. Operated under a cooperative agreement with the University of California, San Diego, this large clinical trials consortium comprises more than 75 sites throughout the United States and Canada. The ADCS focuses on testing agents that lack patent protection, patented drugs that are marketed for other indications, and novel compounds developed by individuals, academic institutions, and small biotech companies. It also develops new evaluation instruments for clinical trials and innovative approaches to clinical trial design. The group provides infrastructure support to other Federally funded clinical efforts, including ADNI and the Dominantly Inherited Alzheimer Network (DIAN, a study of familial

Alzheimer's). See *www.adcs.org* for a summary of current trials and studies conducted by the ADCS.

National Cell Repository for Alzheimer's Disease (NCRAD). This NIA-funded repository, located at Indiana University Medical Center in Indianapolis, provides resources that help researchers identify the genes that contribute to Alzheimer's and other types of dementia. NCRAD collects and maintains biological specimens and associated data on study volunteers from a variety of sources, primarily from the people enrolled at the ADCs as well as those in ADNI, the ADGC, and other studies. NCRAD also houses DNA samples and data from more than 900 families with multiple members affected by Alzheimer's. Qualified research scientists may apply to NCRAD for samples and data to conduct genetic research. Since it was funded 20 years ago, more than 50,000 biological samples have been requested and sent to investigators across the United States, resulting in more than 200 scientific publications, 33 of which were issued in 2010. For more information on NCRAD, go to *http://ncrad.iu.edu.*

NIA Genetics of Alzheimer's Disease Data Storage Site (NIAGADS). Located at the University of Pennsylvania, NIAGADS is a Web-based data warehouse for Alzheimer's disease genetic data. All genetic data derived from NIA-funded studies on the genetics of late-onset Alzheimer's are deposited at NIAGADS, another NIA-approved site, or both. Data from GWAS that are stored at NIAGADS are also made available through the database of Genotype and Phenotype (dbGaP) at the National Library of Medicine's National Center for Biotechnology Information, which was developed to archive and distribute the results of large-scale GWAS analyses. Through dbGaP, data sets from multiple GWAS done on different platforms can be merged, and data from thousands of study participants can be analyzed together, increasing the probability of gene discovery.

Major NIA program initiatives include:

Alzheimer's Disease Neuroimaging Initiative (ADNI). The NIA in 2004 launched this groundbreaking initiative, the largest public-private partnership to date in Alzheimer's disease research. The goal was to find neuroimaging and other biological markers that could be used to detect disease progression and measure the effectiveness of potential therapies. The study recruited 800 participants, a mix of cognitively healthy people and those with Alzheimer's disease or MCI. To speed the pace of analysis and findings, ADNI investigators agreed to make their collected data widely available. MRI and PET scan brain images as well as clinical, genetic, and fluid biomarker data are available to qualified researchers worldwide through a Web-based database.

The first phase of ADNI was remarkably fruitful: more than 170 papers using ADNI data have been published from investigators around the world, and many more will come as more data are collected and analyzed. Early findings have generated excitement about using brain and fluid markers to identify people at risk for developing Alzheimer's or to characterize the pace of deterioration. Accomplishments include new findings about how changes in the structure of the hippocampus may help detect disease progression and effectiveness of potential treatments, and the establishment of biomarker and imaging measures that predict risk for cognitive decline and conversion to dementia. The success of ADNI has inspired similar efforts in Europe, Japan, and Australia.

A follow-on effort, ADNI-GO, was launched with American Recovery and Reinvestment Act funds in 2009, followed by ADNI 2 in fall 2010. ADNI 2 set a 5-year goal of recruiting approximately 1,000 people, age 55 to 90, at 55 sites in the United States and Canada. They will be followed to define changes in brain structure and function as people transition from normal cognitive aging to MCI, and from MCI to Alzheimer's dementia. The study will use imaging techniques and biomarker measures in blood and cerebrospinal fluid specially developed to track changes in the living brain. Researchers hope to identify who is at risk for Alzheimer's, track progression of the disease, and devise tests to measure the effectiveness of potential interventions. ADNI 2 will continue to follow participants in the other ADNI cohorts.

Dominantly Inherited Alzheimer's Disease Network (DIAN). In 2008, the NIA launched the 6-year DIAN study to better understand the biology of early-onset Alzheimer's, a rare, inherited form of the disorder that can occur in people as early as their 30s and 40s. Scientists involved in this collaborative, international effort hope to recruit 300 adult children of people with Alzheimer's disease to help identify the sequence of brain changes that take place even before symptoms of the disorder appear. By understanding this process, researchers hope to gain additional insights into the more common late-onset form of the disease.

Until DIAN, the rarity of the condition and geographic distances between patients and research centers hindered research. Today, volunteers age 18 and older with at least one biological parent with the disorder are participating in DIAN at a network of research sites in the United States, England, and Australia. Each participant receives a range of assessments, including genetic analysis, cognitive testing, and brain scans, and donates blood and CSF so scientists can test for biomarkers. DIAN researchers are building a shared database of the assessment results, samples, and images to advance knowledge of the brain mechanisms involved in Alzheimer's, eventually leading to targets for therapies that can delay or even prevent progress of the disease.

The study is being led by the ADC at Washington University School of Medicine in St. Louis. Research collaborators include Massachusetts General Hospital; Brigham and Women's Hospital; Brown University; Columbia University; Indiana University; the University of California, Los Angeles; the University College, London Institute of Neurology at Queen's Square; and a consortium of the Universities of Melbourne and New South Wales and Edith Cowan University in Australia. For more information about DIAN, go to *www.dian-info.org.*

Alzheimer's Disease Genetics Initiative (ADGI) and Alzheimer's Disease Genetics Consortium (ADGC). The study of Alzheimer's disease genetics is complicated by the likelihood that the risk of late-onset Alzheimer's is influenced by many genes, each of which probably confers a relatively small risk. Identifying these genes requires analyzing the genomes of large numbers of people. ADGI was launched in 2003 to identify at least 1,000 families containing multiple members who have late-onset Alzheimer's as well as family members who do not. In 2009, the NIA funded the ADGC to support the use of large-scale, high-throughput genetics technologies needed by researchers studying late-onset Alzheimer's.

These initiatives are achieving important results. In April 2011, an ADGC-led study confirmed one gene variant and identified several others that may be risk factors for late-onset Alzheimer's disease, the most common form of the disorder. In the largest GWAS ever conducted in Alzheimer's research, investigators studied DNA samples from more than 56,000 study participants and analyzed shared datasets to detect gene variations that may have subtle effects on Alzheimer's risk. In addition to providing

additional insight into the pathology of Alzheimer's and suggesting therapeutic targets, these new gene discoveries may also one day help predict who is at risk for the disease.

Alzheimer's Disease Translational Research Program. Launched in 2004, this program supports early drug discovery and preclinical drug development research by academic scientists and small biotechnology companies, with the goal of finding ways to treat and prevent Alzheimer's, MCI, and age-related cognitive decline. This effort is broadening the range of potential treatments and therapeutic targets by supporting critical steps of the drug discovery process that are traditionally not supported by the pharmaceutical industry. In 2009, the NIA committed 5 million dollars to continue two funding initiatives for early drug discovery and preclinical drug development through 2012.

Alzheimer's Disease Pilot Clinical Trials Initiative. This initiative, begun in 1999, is aimed at increasing the number and quality of preliminary clinical evaluation of interventions for Alzheimer's, MCI, and age-associated cognitive decline. The goal is not to duplicate or compete with the efforts of pharmaceutical companies but to encourage, complement, and accelerate the process of testing new, innovative, and effective treatments. Initially focused on drug interventions, the program has been broadened to nonpharmacologic as well as pharmacologic interventions. NIH sister institutes—the National Center for Complementary and Alternative Medicine and the National Institute of Neurological Disorders and Stroke—also participate in this initiative.

Research Partnership on Cognitive Aging. Through the Foundation for NIH, NIA and the McKnight Brain Research Foundation convened a Cognitive Aging Summit in 2007 focused on healthy brain aging and function. This summit helped galvanize the field and served as a catalyst for two subsequent research initiatives. The first initiative is testing pilot interventions to reverse age-related decline or maintain successful function. The second initiative is determining the neural and behavioral profiles of age-related cognitive change and identifying components of these profiles that distinguish normal age-related change from pathological decline. Investigators heading these pilot studies have met annually to share their initial findings and to receive feedback from their colleagues on this exciting area of research. A second Summit, held in October 2010, shared progress from studies and identified future research directions. Investigators supported by the partnership have had 30 papers published in scientific journals.

NIH Toolbox for Assessment of Neurological and Behavioral Function. Supported by the NIH Blueprint for Neuroscience Research and the NIH Office of Behavioral and Social Sciences Research, researchers are developing a set of brief tests to assess cognitive, sensory, motor, and emotional function, particularly in studies that enroll many people (such as epidemiological studies and clinical trials). Developed under a contract with NIH, these royalty-free tests will be available in English and Spanish and applicable for use in people age 3 to 85 years, enabling direct comparison of cognitive and other abilities at different ages across the lifespan. Now in the final stages of development, this NIH Toolbox resource will be available to researchers and clinicians in fall 2012.

Human Connectome Project. Supported through the NIH Blueprint for Neuroscience Research, the Human Connectome Project was started in 2010 to develop and share knowledge about the structural and functional connectivity of the healthy human brain. This collaborative effort will use cutting-edge neuroimaging instruments, analysis tools, and informatics technologies to map the neural pathways underlying human brain function. The project will map the connectomes in 1,200 healthy adults—twin pairs and their siblings—and will study anatomical and functional connections between regions of the brain. This information will be related to behavioral test data collected using another NIH Blueprint research tool, the NIH Toolbox for Assessment of Neurological and Behavioral Function, and to data on the genetic makeup of the participants. The goal is to reveal the contributions of genes and environment in shaping brain circuitry and the variability in such connectivity. The human connectome map of the healthy adult brain will serve as a foundation to further understand how brain networks change with age and neurological diseases like Alzheimer's.

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