ALZHEIMER'S DISEASE
Unraveling the Mystery
Preface

Over the past few decades, Alzheimer’s disease (AD) has emerged from obscurity. Once considered a rare disorder, it is now seen as a major public health problem that has a severe impact on millions of older Americans and their families. The National Institute on Aging (NIA) is the lead agency for AD research at the National Institutes of Health (NIH). NIA launched its AD program in 1978, and since then, the study of this disease has become one of NIA’s top priorities. Several other NIH institutes also conduct and sponsor studies on AD.

Thanks to the work of NIH institutes, other research organizations around the world, and many private-sector research, education, and advocacy groups, the study of AD is moving ahead rapidly. This book explains what AD is, describes the main areas in which researchers are working, and highlights new approaches for helping families and friends care for people with AD.

TO GET THE MOST OUT OF THIS BOOK

Learn the Basics of the Healthy Brain

- The parts of the brain (pages 10-13)
- How neurons work (pages 14-16)
- The changing brain in healthy aging (pages 17-19)

Discover What Happens to the Brain in AD

- The hallmarks of AD (pages 21-26)
- The changing brain in AD (pages 27-33)

Explore Cutting-Edge AD Research

- Looking for causes (pages 36-47)
- Diagnosing AD (pages 48-53)
- Searching for treatments (pages 54-61)

Learn about Caregiver Support

- Who are AD caregivers? (page 63)
- Reducing the personal costs of caregiving (pages 64-67)
- Taking care of mom or dad from a distance (page 68)

TO LEARN EVEN MORE

Visit NIA’s Alzheimer’s Disease Education and Referral Center website at www.nia.nih.gov/alzheimers. There, you will find resources to accompany this book, such as downloadable versions of the illustrations and an animation that shows what happens to the changing brain in AD. And while you are there, explore the ADEAR Center’s many other offerings. These include free publications about AD and AD caregiving, clinical trials information, and a list of NIA-funded Alzheimer’s Disease Centers.
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"Never have I loved my husband of 41 years more than I do today....Though he may not know I’m his wife, he does know that my presence means his favorite foods and drinks are near at hand....I wonder why I can sit daily by his side as I play tapes, relate bits and pieces of news, hold his hand, tell him I love him. Yet I am content when I am with him, though I grieve for the loss of his smile, the sound of my name on his lips.”

This excerpt from *Lessons Learned: Shared Experiences in Coping*, by participants of the Duke University Alzheimer Support Groups, gives a glimpse into what a person with Alzheimer’s disease (AD) and a family caregiver might experience as the disease progresses. The gradual slipping away of mind and memory is frightening and frustrating, both for the person with the disease and for family and friends, and can elicit strong feelings of love, grief, anger, and exhaustion.

AD is an irreversible, progressive brain disease that slowly destroys memory and thinking skills, eventually even the ability to carry out the simplest tasks. In most people with AD, symptoms first appear after age 60. AD is caused by a disease that affects the brain. In the absence of disease, the human brain often can function well into the 10th decade of life.

Not so long ago, we were not able to do much for people with AD. Today, that situation is changing. Thousands of scientists, voluntary organizations, and health care professionals are studying AD so that they can find ways to manage, treat, and one day prevent this terrible disease.

**AD: A GROWING NATIONAL PROBLEM**

For many older adults and their families, AD stands in the way of the “Golden Years.” It also presents a major problem for our health care system and society as a whole. AD is the most common cause of dementia among older people. Recent estimates of how many people in the United States currently have AD differ, with numbers ranging from 2.4 million to 4.5 million, depending on how AD is measured. But scientists agree that unless the disease can be effectively treated or prevented, the numbers will increase significantly if current population trends continue.

Our aging society makes AD an especially critical issue. A 2005 Census Bureau report on aging in the United States notes that the population age 65 and older is expected to double in size to about 72 million people within the next 25 years. Moreover, the 85 and older age group is now the fastest growing segment of the population. This is all the more important for a neurodegenerative...
Like AD, other forms of dementia occur when brain cells start to die and the disease process begins many years, perhaps even decades, before symptoms emerge. Discovering ways to identify Alzheimer’s in the earliest stages and halt or slow its progress will benefit individuals, families, and the Nation as a whole.

**ABOUT THIS BOOK**

Thinking about Alzheimer’s leads to questions such as: What causes it? What can be done to cure it or prevent it? Will I get it? Scientists ask the same types of questions, and this book describes their search for answers. It is written for people with Alzheimer’s, their family members and friends, caregivers, and others interested in Alzheimer’s.

This book has four sections:

- **Part 1** gives readers some basics about the healthy brain. Illustrations and text show what a healthy brain looks like and how it works.
- **Part 2** focuses on what happens in the brain during Alzheimer’s.

Visit the National Institute on Aging (NIA) Alzheimer’s Disease Education and Referral (ADEAR) Center website at [www.nia.nih.gov/alzheimers/alzheimers-disease-video](http://www.nia.nih.gov/alzheimers/alzheimers-disease-video) to view an animation that helps this part of the book come alive.
Part 3 talks about current research and the advances that are bringing us closer to ways of managing and eventually defeating AD. Part 4 focuses on issues important to AD caregivers and families, including current research that is finding ways to improve caregiver support.

The end of the book includes a list of publications and resources that people with AD, family members, and caregivers may find useful as they live day to day with the disease.

A book like this is possible only because of the major progress that scientists throughout the world have made. Not long ago, we knew very little about AD other than some facts about its major characteristics. Today, we are beginning to understand more about what AD is and who gets it, how and why it develops, and what course it follows. We are learning about the complex interface between AD and normal age-related changes in the brain. We also are getting much

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Then and Now: The Fast Pace of Developments in AD Research

As shown in this timeline, we have learned a lot since Dr. Alzheimer presented the case of his patient, Auguste D. The pace of research continues to accelerate as new findings open more and more doors to discovery.

1906
- Dr. Alois Alzheimer, a German neurologist and psychiatrist, describes the case of a 51-year-old woman, Auguste D., who had been admitted to a hospital 5 years earlier with a cluster of unusual symptoms, including problems with comprehension and memory, an inability to speak, disorientation, behavioral problems, and hallucinations. After her death, Dr. Alzheimer examined her brain tissue and described two of the hallmarks of AD—numerous globs of sticky proteins in the spaces between neurons (beta-amyloid plaques) and a tangled bundle of fibrils within neurons (neurofibrillary tangles).

1910s – 1940s
- Belief persists that “senile dementia” is a normal part of aging.

1950s
- Scientists study the biological structure of plaques and tangles.

1960s
- Scientists discover a link between dementia and the number of plaques present in the brain. AD is recognized as a distinct disease, not a normal part of aging.

1970s
- Scientists find that levels of acetylcholine, a neurotransmitter important in memory formation, falls sharply in people with AD. This discovery is one of the first to link AD with biochemical changes in the brain.
- “Alzheimer’s disease” becomes a common term as recognition of AD as a major public health problem grows.
- NIA is established.

1980s
- Diagnostic criteria for AD are established.
- Genetic links to early-onset AD begin to surface.
- Congress mandates NIA as lead Federal agency for AD research.
better at diagnosing it early and accurately. Most important, we now have some promising leads on possible treatments. Studies also are beginning to focus on preventive strategies by examining lifestyle factors that might influence a person’s risk of developing AD.

Since the 1970s, research supported by NIA and other organizations has deepened our understanding of this devastating disease. It also has expanded our knowledge of brain function in healthy older people and identified ways we might lessen normal age-related declines in mental function. Most importantly, this accumulated research has increased our appreciation for just how complex AD is. It is now clear that many scientific and clinical disciplines need to work together to untangle the genetic, biological, and environmental factors that, over many years, set a person on a course that ultimately results in AD.

Scientists start to unravel the biological pathways that lead to the development of beta-amyloid plaques in the brain.
- Abnormal tau protein in tangles is identified.

1990s
- The U.S. Food and Drug Administration (FDA) approves tacrine (Cognex®), the first drug used to treat AD. This drug has since been replaced by other medications.
- Genetic mutations linked to early-onset and late-onset AD are discovered.
- The first transgenic mouse model of AD is created.
- Additional diagnostic criteria are developed for AD.
- Characteristics of mild cognitive impairment are described and defined.
- NIA launches the Alzheimer’s Disease Education and Referral Center, AD Cooperative Study, and other initiatives to conduct and support AD treatment and prevention clinical trials.

2000s
- The FDA approves other AD drugs, including rivastigmine (Exelon®), galantamine (Razadyne®), donepezil (Aricept®), and memantine (Namenda®) to treat symptoms of AD.
- Early work on an AD vaccine begins.
- Many new AD clinical trials, initiatives, and studies are launched, looking at a broad array of translational, treatment, and prevention issues.
- New transgenic mouse models, including one that develops both plaques and tangles, are developed.
- Pittsburgh Compound B (PiB) is developed, allowing researchers to “see” beta-amyloid plaques in the brains of living people.
- The growing sophistication of neuroimaging techniques, genetics, memory and cognitive tests, structured interviews, and other technologies improve our ability to identify people at high risk of AD.
The Basics of the Healthy Brain
To understand AD, it is important to know a bit about the brain. This part of Unraveling the Mystery gives an inside view of the normal brain, how it works, and what happens during aging.

The brain is a remarkable organ. Seemingly without effort, it allows us to carry out every element of our daily lives. It manages many body functions, such as breathing, blood circulation, and digestion, without our knowledge or direction. It also directs all the functions we carry out consciously. We can speak, hear, see, move, remember, feel emotions, and make decisions because of the complicated mix of chemical and electrical processes that take place in our brains.

The brain is made of nerve cells and several other cell types. Nerve cells also are called neurons. The neurons of all animals function in basically the same way, even though animals can be very different from each other. Neurons survive and function with the help and support of glial cells, the other main type of cell in the brain. Glial cells hold neurons in place, provide them with nutrients, rid the brain of damaged cells and other cellular debris, and provide insulation to neurons in the brain and spinal cord. In fact, the brain has many more glial cells than neurons—some scientists estimate even 10 times as many.

Another essential feature of the brain is its enormous network of blood vessels. Even though the brain is only about 2 percent of the body’s weight, it receives 20 percent of the body’s blood supply. Billions of tiny blood vessels, or capillaries, carry oxygen, glucose (the brain’s principal source of energy), nutrients, and hormones to brain cells so they can do their work. Capillaries also carry away waste products.

### The Brain’s Vital Statistics

<table>
<thead>
<tr>
<th><strong>ADULT WEIGHT</strong></th>
<th>about 3 pounds</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ADULT SIZE</strong></td>
<td>a medium cauliflower</td>
</tr>
<tr>
<td><strong>NUMBER OF NEURONS</strong></td>
<td>about 100,000,000,000 (100 billion)</td>
</tr>
<tr>
<td><strong>NUMBER OF SYNAPSES</strong></td>
<td>(the gaps between neurons) about 100,000,000,000,000 (100 trillion)</td>
</tr>
<tr>
<td><strong>NUMBER OF CAPILLARIES</strong></td>
<td>(tiny blood vessels) about 400,000,000,000,000 (400 billion)</td>
</tr>
</tbody>
</table>
The brain has many parts, each of which is responsible for particular functions. The following section describes a few key structures and what they do.

**THE MAIN PLAYERS**
- Two cerebral hemispheres account for 85 percent of the brain’s weight. The billions of neurons in the two hemispheres are connected by thick bundles of nerve cell fibers called the corpus callosum. Scientists now think that the two hemispheres differ not so much in what they do (the “logical versus artistic” notion), but in how they process information. The left hemisphere appears to focus on details (such as recognizing a particular face in a crowd). The right hemisphere focuses on broad background (such as understanding the relative position of objects in a space). The cerebral hemispheres have an outer layer called the cerebral cortex. This is where the brain processes sensory information received from the outside world, controls voluntary movement, and regulates cognitive functions, such as thinking, learning, speaking, remembering, and making decisions. The hemispheres have four lobes, each of which has different roles:
  - The frontal lobe, which is in the front of the brain, controls “executive function” activities like thinking, organizing, planning, and problem solving, as well as memory, attention, and movement.
  - The parietal lobe, which sits behind the frontal lobe, deals with the perception and integration of stimuli from the senses.
  - The occipital lobe, which is at the back of the brain, is concerned with vision.
  - The temporal lobe, which runs along the side of the brain under the frontal and parietal lobes, deals with the senses of smell, taste, and sound, and the formation and storage of memories.
- The cerebellum sits above the brain stem and beneath the occipital lobe. It takes up a little more than 10 percent of the brain. This part of the brain plays roles in balance and coordination. The cerebellum has two hemispheres, which receive information from the eyes, ears, and muscles and
This illustration shows a three-dimensional side view of one of two cerebral hemispheres of the brain. To help visualize this, imagine looking at the cut side of an avocado sliced long ways in half, with the pit still in the fruit. In this illustration, the "pit" is several key structures that lie deep within the brain (the hypothalamus, amygdala, and hippocampus) and the brain stem.
joints about the body’s movements and position. Once the cerebellum processes that information, it sends instructions to the body through the rest of the brain and spinal cord. The cerebellum’s work allows us to move smoothly, maintain our balance, and turn around without even thinking about it. It also is involved with motor learning and remembering how to do things like drive a car or write your name.

- The **brain stem** sits at the base of the brain. It connects the spinal cord with the rest of the brain. Even though it is the smallest of the three main players, its functions are crucial to survival. The brain stem controls the functions that happen automatically to keep us alive—our heart rate, blood pressure, and breathing. It also relays information between the brain and the spinal cord, which then sends out messages to the muscles, skin, and other organs. Sleep and dreaming are also controlled by the brain stem.

**OTHER CRUCIAL PARTS**

Several other essential parts of the brain lie deep inside the cerebral hemispheres in a network of structures called the **limbic system**. The limbic system links the brain stem with the higher reasoning elements of the cerebral cortex. It plays a key role in developing and carrying out instinctive behaviors and emotions and also is important in perceiving smells and linking them with memory, emotion, and instinctive behaviors. The limbic system includes:

- The **amygdala**, an almond-shaped structure involved in processing and remembering strong emotions such as fear. It is located in the temporal lobe just in front of the hippocampus.
- The **hippocampus**, which is buried in the temporal lobe, is important for learning and short-term memory. This part of the brain is thought to be the site where short-term memories are converted into long-term memories for storage in other brain areas.
- The **thalamus**, located at the top of the brain stem, receives sensory and limbic information, processes it, and then sends it to the cerebral cortex.
- The **hypothalamus**, a structure under the thalamus, monitors activities such as body temperature and food intake. It issues instructions to correct any imbalances. The hypothalamus also controls the body’s internal clock.

**THE BRAIN IN ACTION**

Sophisticated brain-imaging techniques allow scientists to monitor brain function in living people and to see how various parts of the brain are used for different kinds of tasks. This is opening up worlds of knowledge about brain function and how it changes with age or disease.

One of these imaging techniques is called **positron emission tomography**, or PET scanning. Some PET scans measure blood flow and glucose metabolism throughout the brain. (For more on metabolism, see page 16.) During a PET scan, a small amount of a radioactive substance is attached to a compound, such as glucose, and injected into the bloodstream. This tracer substance eventually goes to the brain. When nerve cells in a region of the brain become active, blood flow and glucose metabolism in that region increase. When colored to reflect metabolic activity, increases usually look red and yellow. Shades of blue and black indicate decreased or no activity within a brain region.
In essence, a PET scan produces a “map” of the active brain.

Scientists can use PET scans to see what happens in the brain when a person is engaged in a physical or mental activity, at rest, or even while sleeping or dreaming. Certain tracers can track the activity of brain chemicals, for example neurotransmitters such as dopamine and serotonin. (To learn about exciting developments using one new tracer, see PiB and PET on page 28.) Some of these neurotransmitters are changed with age, disease, and drug therapies.
The human brain is made up of billions of neurons. Each has a cell body, an **axon**, and many **dendrites**. The cell body contains a **nucleus**, which controls much of the cell’s activities. The cell body also contains other structures, called organelles, that perform specific tasks.

The axon, which is much narrower than the width of a human hair, extends out from the cell body. Axons transmit messages from neuron to neuron. Sometimes, signal transmissions—like those from head to toe—have to travel over very long distances. Axons are covered with an insulating layer called **myelin** (also called white matter because of its whitish color). Myelin, which is made by a particular kind of glial cell, increases the speed of nerve signal transmissions through the brain.

Dendrites also branch out from the cell body. They receive messages from the axons of other neurons. Each neuron is connected to thousands of other nerve cells through its axon and dendrites.

Groups of neurons in the brain have special jobs. For example, some are involved with thinking, learning, and memory. Others are responsible for receiving information from the sensory organs (such as the eyes and ears) or the skin. Still others communicate with muscles, stimulating them into action.

Several processes all have to work smoothly together for neurons, and the whole organism, to survive and stay healthy. These processes are communication, metabolism, and repair.

**COMMUNICATION**

Imagine the many miles of fiber-optic cables that run under our streets. Day and night, millions of televised and telephonic messages flash at incredible speeds, letting people strike deals, give instructions, share a laugh, or learn some news. Miniaturize it, multiply it many-fold, make it much more complex, and you have the brain. Neurons are the great communicators, always in touch with their neighbors.

Neurons communicate with each other through their axons and dendrites. When a dendrite receives an incoming signal (electrical or chemical), an “action potential,” or nerve impulse, can be generated in the cell body. The action potential travels to the end of the axon and once there, the passage of either electrical current or, more typically, the release of chemical messengers, called neurotransmitters, can be triggered. The neurotransmitters are released from the axon terminal and move across a tiny gap, or **synapse**, to specific receptor sites on the receiving, or postsynaptic, end of dendrites of nearby neurons. A typical neuron has thousands of synaptic connections, mostly on its many dendrites, with other neurons. Cell bodies also have receptor sites for neurotransmitters.
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