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Alzheimer's Disease Yesterday, Today and Tomorrow: Progress and Challenges

by Maria C. Carrillo



Alzheimer's Disease Yesterday

The year 2006 marked the 100th anniversary of a small medical meeting in Germany, where physician Alois Alzheimer presented the haunting case of Auguste D.

Alzheimer first saw Auguste in 1901 following her admission at age 51 to the psychiatric hospital where he worked. She was plagued by symptoms that did not fit any known diagnosis: rapidly failing memory, confusion, disorientation, trouble expressing her thoughts and unfounded suspicions about her family and the hospital staff.

After four years of steady decline that left her bedridden and mute, Auguste died and Alzheimer performed an autopsy. In her brain, he found dramatic shrinkage, widespread dead and dying cells and two kinds of microscopic deposits he'd never seen before.

"All in all," Alzheimer wrote in his presentation abstract, "we are obviously faced obviously with a peculiar disease process."

This mysterious, devastating disorder soon entered the medical literature as "Alzheimer's disease." The unusual brain deposits gained

recognition as its pathological hallmarks and became known as "plaques" and "tangles."

In 1915, Alois Alzheimer himself died at age 51, never suspecting that his encounter with Auguste D. would one day touch the lives of millions and drive a massive international research effort. Today, we know that more than 5 million Americans have Alzheimer's disease, according to the Alzheimer's Association's 2007 Alzheimer's Disease Facts and Figures. This number is expected to soar as high as 7.7 million by 2030.

Alzheimer's Disease Today

The course of the disease today remains much the same as Dr. Alzheimer described in 1906. Alzheimer's is a progressive brain disorder that gradually destroys a person's memory and ability to learn, reason, make judgments, communicate and carry out daily activities. As Alzheimer's progresses, individuals may also experience such changes in personality and behavior as anxiety, suspiciousness and agitation, as well as delusions or hallucinations. Most individuals with Alzheimer's eventually require a higher level of care than friends and family can provide at home.

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The brains of people with Alzheimer's have an abundance of plaques and tangles, the two hallmark abnormal structures Dr. Alzheimer first saw in his patient. Plaques consist chiefly of a protein called beta-amyloid that builds up into dense deposits outside and around neurons, or nerve cells. Neurons are the main cells involved in the brain's vast network that processes, stores and retrieves information. Eventually, plaques disrupt cell-to-cell communication and trigger neuron degeneration and death.

Tangles are abnormally twisted fibers of another protein found inside neurons. They destroy a vital internal cellular "scaffold" involved in moving food molecules and essential components around the cell. Collapse of this "scaffolding" is another factor in cell disruption and death.

Although we easily recognize the symptoms described by Alois Alzheimer 100 years ago in the disease we see today, we also see important differences. Dr. Alzheimer had no treatment or special care to offer Auguste D. Now, there are

five drugs specifically approved by the U.S. Food and Drug Administration (FDA) to treat symptoms of the disease. There are also many types of services and support and an array of special long-term care options designed to meet the unique needs of individuals like Auguste with cognitive impairment.

We also have learned that age is the greatest risk factor for Alzheimer's disease. The prevalence of the disease doubles about every five years after age 65, and reaches nearly 50 percent over age 85. In addition, there are at least 200,000 Americans who, like Auguste D., develop Alzheimer's when they are younger than 65.

Scientists have identified several risk factors in addition to age. There is a strong link between serious head injury involving loss of consciousness and future risk of Alzheimer's. There is also a very strong heart-head connection: what's good for your heart is good for your brain. This connection exists because the brain is nourished by one of the body's richest networks of blood vessels. Each heartbeat pumps about 20 to 25 percent of your blood to your head, where brain cells use at least 20 percent of the nutrients and oxygen that blood carries. The risk of developing Alzheimer's or vascular dementia, a related disorder, appears to be increased by high blood pressure, heart disease, stroke, diabetes and high cholesterol.

Other lines of evidence suggest that strategies for overall healthy aging may help keep the brain healthy and may even offer some protection against Alzheimer's. It's important to keep weight within recommended guidelines, avoid tobacco and excess alcohol, stay socially connected and exercise both the body and the mind.

Genes (heredity) play a role in Alzheimer's. Researchers have linked two categories of genes to the disease: 1) deterministic genes, which directly cause the disease and guarantee that an individual who inherits one will develop Alzheimer's; and 2) risk genes, which increase the likelihood a person will develop Alzheimer's but do not guarantee it will happen.

Deterministic Alzheimer genes are rare, accounting for less than 5 percent of cases. This

type of Alzheimer's is called familial Alzheimer's disease and has been found in only a few hundred extended families worldwide. In familial Alzheimer's, family history shows that many relatives over multiple generations are affected. It tends to strike at an unusually young age, possibly as early as age 30 or 40.

Risk genes increase the likelihood of developing Alzheimer's disease but do not guarantee it will occur. The risk gene most strongly linked to Alzheimer's is called APOE-e4. It is one of three common forms of a gene providing the blueprint for apolipoprotein E, a protein that helps transport cholesterol in the bloodstream. Those who inherit one copy of APOE-e4 have an increased risk of Alzheimer's, and those who inherit two copies have an even higher risk. But risk does not equal certainty. Many individuals with one or two copies of APOE-e4 never develop Alzheimer's, and Alzheimer's often occurs in those with no APOE-e4. Scientists believe there may be at least a dozen other risk genes in addition to APOE4. More research is needed to determine the exact role APOE-e4 plays in Alzheimer's and to identify other risk genes.

Another important development is our ability to diagnose Alzheimer's disease accurately early in the course of the disease. Early diagnosis is very important for medical, practical and scientific reasons. Medically, early diagnosis enables a person to take advantage of current treatments and supportive services while they may be most effective. Practically, early diagnosis gives the person and family a framework for understanding symptoms and can spur planning for the future, making appropriate living arrangements and designating health care proxy and power of attorney.

Scientifically, early diagnosis plays a critical role in paving the way to next-generation treatments and will hopefully mean a brighter future for those diagnosed with Alzheimer's disease.

Alzheimer's Disease Tomorrow

The biggest change on the Alzheimer horizon is the accelerating effort to develop next-

generation drugs with the potential to stop or prevent the underlying death and destruction of nerve cells. Early diagnosis sets the stage for a person to consider participating in a clinical study of one of these promising new treatments.

Nearly a dozen different experimental compounds have reached Phase III clinical trials, the most advanced stage of testing investigational drugs. The FDA typically considers data from at least two Phase III trials, in addition to results of earlier-phase studies, when considering a new drug for approval in general medical practice. Virtually all of these clinical studies seek to recruit individuals in early Alzheimer stages, when experimental disease-modifying drugs may show their greatest benefit.

Participation in research can give individuals and families a sense of purpose and meaning by contributing to scientific knowledge that may help answer important questions about Alzheimer's and bring us closer to effective treatments. In addition, research shows that study participants tend to do better, on average, than individuals in a similar stage of the disease who are not enrolled in a study. Scientists believe this advantage may result from the state-of-the-art care participants receive, regardless of whether they are assigned to receive the experimental treatment or the placebo (inactive, look-alike treatment).

In addition to investigating next-generation treatments, clinical studies are exploring ways to push the diagnostic threshold back even earlier in the disease process. Tests are being developed to detect the earliest signs of Alzheimer's in urine, blood, cerebrospinal fluid or the eye. Other promising emerging diagnostic technologies include brain imaging with magnetic resonance imaging (MRI) and position emission tomography (PET).

No Time to Lose

Although the future—with regard to preventing Alzheimer's disease—has never looked brighter, we are in an urgent race against time. In 2006, baby boomers (those born between 1946 and 1964) began turning 60 at the rate of 330

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per hour, according to the U.S. Census Bureau. In 2011, boomers begin turning 65, reaching the age of greatest risk for Alzheimer's.

Data from 2007 Alzheimer's Disease Facts and Figures show that today, someone in the United States develops Alzheimer's disease every 72 seconds; by mid-century, an American could develop Alzheimer's every 33 seconds.

Facts and Figures further shows that U.S. deaths attributed to Alzheimer's are rising dramatically while deaths caused by prostate and breast cancers, heart disease and stroke are falling.

Medicare currently spends nearly three times as much for people with Alzheimer's and other dementias as for the average beneficiary with no cognitive impairment. Overall, Medicare costs are projected to double from \$91 billion in 2005 to more than \$189 billion by 2015, more than the current gross national product of 86 percent of the world's countries. In 2005, state and federal Medicaid spending for nursing home and home care for people with Alzheimer's and other dementias was estimated at \$21 billion; that number is projected to increase to \$27 billion by 2015.

The economic costs to families are also great. According to an AARP analysis, Medicare beneficiaries age 65 and older spent an average of \$3,455 (22 percent) of their income on health care in 2003. About 45 percent of those expenses were for Medicare Part B premiums, private Medicare plans and private supplemental insurance. Medicare beneficiaries age 65-plus paid 37 percent of the cost of nursing home care out-of-pocket in 2002, the most recent year for which expenditure figures are available by type of medical service. Out-of-pocket expenditures for health and long-term care are higher, on average, for older people with Alzheimer's and other dementias than for other seniors.

It is clear that we need to accelerate progress in current promising directions and continue to identify new paths to success. As the world's largest private, nonprofit funder of Alzheimer research, the Alzheimer's Association has committed \$220 million to promising lines of inquiry. The Association advocates diligently for greater public funding of research through the National Institutes of Health (NIH) and other government agencies. The association believes that an NIH investment of \$1 billion dollars per year would empower the scientific community to capitalize on current findings and achieve the necessary acceleration of progress in the field. *

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