The End of Memory: Alzheimer's Disease and Research to Develop Innovative Treatment

Erez Podoly
The Department of Biochemistry and the Wolfson Center for Applied Structural Biology, Hebrew University of Jerusalem

"...There is no remembrance of things past. Ecclesiastes..." 1:11

For there is no remembrance... for ever; seeing that in the days to come all will have been long forgotten. Ecclesiastes 2:16

No one waited for Dr. Alzheimer to define the disease. Thousands of years before he did so in the twentieth century, the writers of religious texts grasped the bitter truth that human memory fades over time and, most important, that aging and gradual memory loss are inextricably linked.

We can pinpoint a moment when Alzheimer's disease burst, full-strength, into the public consciousness. It was when Ronald Reagan, following his term as fortieth president of the United States, held a small model of the White House and was asked to identify it. He reportedly replied, "It has something to do with me, but I'm not sure what."

We are made of the things we remember. Our identity, our past, the people we love—all of these are an inseparable part of our brain's ability to connect very fine threads together into a complete tapestry. And that is not just a metaphor. It is an apt description of the processes that are damaged in the brains of Alzheimer's victims.

What, then, is Alzheimer's disease? Alzheimer's is a degenerative, incurable disease marked by a progressive decline in brain activity that leads to a gradual loss of memory, reasoning ability, and personality (dementia), and, eventually to death.

A Brief History

In 1901, a woman about 50 years old named Auguste D. was a patient at a mental hospital in Frankfurt, Germany. She evidenced language and cognitive breakdowns, delusions, paranoia, and aggressive behavior. Following her death in 1906, her brain was analyzed by one of the physicians at the hospital, Dr. Alois Alzheimer (1864–1915). Alzheimer presented his findings at a psychiatric conference and published them later that same year. While Alzheimer did not discover the disease, he was the first to draw a connection between pathological and clinical changes that accompany dementia. As early as 1910, the cause of dementia was referred to as "Alzheimer's disease."

Physiological Features of the Disease

The key contribution of Dr. Alzheimer's analysis was to describe the characteristics of a brain afflicted by the disease and to develop a technique for identifying these markers. What he found were clumps and knots of brains cells, now referred to, respectively, as amyloid plaques and neurofibrillary tangles.

1. Amyloid plaques

People with Alzheimer's develop toxic plaques surrounding brain cells. These plaques consist of fibers of a protein called amyloid beta (Aβ), which is a segment of a larger protein, the amyloid precursor protein (APP) formed in our bodies. In a healthy brain, segments of protein are destroyed naturally; in the brains of Alzheimer's victims, APP is cut in a different way, and segments of Aβ accumulate to form insoluble plaques.

2. Neurofibrillary tangles

Another characteristic of an Alzheimer-afflicted brain is fibers of protein (called "tau") within cells that become twisted and insoluble. In a healthy brain, the tau forms part of a tiny network of microtubules that assists the nerve cell structure in carrying nutrients from one part of the nerve cell to another. In the case of Alzheimer's, the tau in the brain is impaired and the microtubule structure destroyed.

There is some dispute over the nature of these two features. Are they responsible for degenerative processes within the brain, or are they the result of damage that has already occurred? Evidence gathered in recent years points to the involvement of both phenomena in causing the disease and indicates that Aβ is actively involved in inflicting the initial damage.

Other Features

Alzheimer's disease results in the death of nerve cells and the loss of brain tissue. The production of acetylcholine—the neurotransmitter of the motor and nerve systems that is responsible for regulating heart activity and breathing—is slowed in the brains of Alzheimer's victims because the nerve cell that produces it degenerates. Over time, the brain diminishes in size dramatically while its ventricles expand. The brain cortex—the outer layer of the brain's cerebral hemisphere, which accounts for over 40 percent of the brain's weight and is directly responsible for awareness, perception, memory, thinking, intellectual ability, intellect, and the initiation of voluntary movements—shrivels and, as a result, becomes inactive. Particularly severe shrinkage occurs in the hippocampus, an area deeper in the brain that plays a crucial role in generating new memories.

Causes of the Disease

The variety of factors triggering the disease indicates the presence of a complex, intricate mechanism that researchers are still far from able to fully understand. The primary risk factor is age. Alzheimer's is, undoubtedly, an old persons' disease. Other known causes are hereditary and dietary (stemming from low levels of folic acid or vitamin B12, or high cholesterol, for example). Infection, disease, and injury are suggested as other causes—thyroid malfunctioning, a lack of zinc or excess of aluminum, high blood pressure, strokes, and head injuries, for example. While some of these causes are better understood than others, the effect of the great majority of them is still clouded in mystery. The causes are also intertwined, making it difficult to consider them separately:

1. Heredity

Alzheimer's has a heredity base. Evidence shows that first-degree relatives of Alzheimer's victims have a 50 percent greater risk of developing the disease in old age, and the risk for the identical twin of an Alzheimer's victim is nearly 90 percent. There are two types of Alzheimer's. The type occurring in old age, which accounts

for 95 percent of all cases, has a complex hereditary pattern. The other, rare type develops at an early age and is caused by mutations of some genes, among them APP1, which is located in chromosome 21. People with Down's syndrome, who have an extra chromosome 21, often develop signs of Alzheimer's in their thirties, perhaps because of the additional APP1 they carry.

2. High cholesterol and a shortage of essential fatty acids
Published research reports that high cholesterol in middle age is a risk factor for Alzheimer's, perhaps because it is linked to excess production of APP. High cholesterol has been shown to increase production of ApoE, which is know to be a characteristic feature of Alzheimer's.

3. Insufficient blood flow in the brain and blood vessels
High blood pressure is a known risk factor for vascular dementia. Small brain infarctions, the result of minor strokes, destroy brain tissue in areas where blood flow has been blocked. High blood pressure can also lead to increased production of Aβ or heighten sensitivity to its damage.

4. Free radicals
Free radicals are chemically active compounds that attach themselves to DNA, proteins, and fats (among other things) and oxidize them. Although oxidation is essential for life, over-oxidation, or mis-targeted oxidation, is harmful. When comparative analyses of brains are performed after death, patients who died of Alzheimer's are found to have higher levels of oxidation by-products than patients who died of other causes.

5. Inflammatory reactions
Nerve cells can die in many ways. Occasionally, the body tries to correct the situation by responding with inflammation and immunization processes that are only likely to worsen the damage. In Alzheimer's, microglia-type immunization cells secrete interleukin-1, an antibody that directly impairs nerve cells in the brain and increases the production of APP. The indirect result of this process is additional nerve damage.

Symptoms
1. Memory loss
2. Difficulty performing routine tasks
3. Language disturbances
4. Disorientation with regard to place and time
5. Impaired judgment
6. Difficulty with abstract thinking
7. Misplacement of objects
8. Mood and behavior changes
9. Personality changes
10. Loss of initiative

Progressive Stages of the Disease
If we picture the human head as a fully lit house, we can compare the progression of Alzheimer's disease to the process of turning off each light, one by one, until there is total darkness. Alzheimer's victims are known to go through seven stages of decline:
1. No memory impairment at all.
2. The individuals note minor lapses in memory: difficulty finding the right word, lost keys or eyeglasses.
3. People in the individuals' immediate environment begin to notice symptoms: misplacement of valuable objects, problems with planning and organization, loss of social skills.
4. In a medical interview, the individuals remember little about recent events or their own personal history. They report problems handling complex tasks such as paying bills, and they have difficulty with complicated mental arithmetic.
5. Day-to-day assistance is required. The individuals cannot remember everyday information such as their address and home phone number. They do not know the date, or even the season of the year (meaning that they need help choosing the proper clothing to wear), and they cannot do simple mental arithmetic.
6. Dramatic personality changes make the individuals totally dependent on others. They tend to be suspicious, have delusions, and/or demonstrate compulsive behavior and therefore require assistance in every aspect of their daily lives. They are unaware of events occurring in their immediate environment and forget important details about themselves. They occasionally fail to recognize the faces or remember the names of familiar people. They cannot dress themselves since they have forgotten the function of each piece of clothing, and they cannot use the toilet without assistance.
7. The individuals lose the ability to speak and move. They cannot swallow, their reflexes do not operate normally, and their muscles grow rigid.
To the hypochondriacs among us: It is normal to occasionally forget where you put the car keys. But if you forget what those keys are for, arrange for a medical examination as soon as possible.

There is no simple and surefire test for diagnosing Alzheimer's. Some physicians choose to perform a brain scan using methods such as magnetic resonance imaging (MRI) or computerized tomography (CT), which may pinpoint visible abnormalities that first appear in the area of information memory loss (the entorhinal cortex), later in the adjacent hippocampus (the brain center crucial to memory and learning, among other things), and finally in the brain cortex, where the damage at this point is extensive. Degenerative signs in these vital areas of the brain are apparent before any signs of cognitive impairment. Although these relatively new scanning techniques may appear to be useful for early detection of Alzheimer's, they have not developed sufficiently to be considered reliable tools for clinical diagnosis.

In practice, Alzheimer's disease is diagnosed by testing memory, language, orientation, and judgment. Physicians also evaluate observable changes in abstract thinking ability, the desire to take initiative, mood or frame of mind, and personality. The delayed recall test, which measures the patients' ability to recall information that they learned or was read to them a short while earlier, is thought to be highly reliable. Another method of diagnosis, not yet commonly used, is to perform a spinal tap to remove fluid that is then tested for the presence of Aβ—an indicator that appears only in cases of Alzheimer's. Changes in the mineral and protein composition of the blood are also used as diagnostic indicators, but this method has not yet proven to have sufficiently scientific grounding. Diagnostic certainty, unfortunately, can only be achieved in an autopsy after death.

The Number of Victims
According to most estimates, nearly 27 million persons in the world are afflicted by Alzheimer's disease. In the U.S. alone, a new case of Alzheimer's is diagnosed every 72 seconds. Alzheimer's follows heart disease, cancer, stroke, and respiratory disease in the list of the most common health-related causes of death in Western industrialized countries. It ranks seventh in general causes of death in the West, and its prevalence is rising rapidly in comparison with the other health-related conditions mentioned, which occur with less frequency over time.

The constantly increasing life span in the Western world has led to Alzheimer's soaring rates among the elderly population. If there is no change in treatment and/or prevention strategies, and if, as anticipated, human life span continues to increase, an estimated one out of 85 persons in the world will be afflicted by the disease by the year 2050—four times the estimated number of victims today. In a reality in which more and more people are living well into their 80s, Alzheimer's is an epidemic. If fact, given its gradual and subtle onset, it is sometimes called "the silent epidemic.".

Medicinal Treatment
Alzheimer's is still classified as an incurable disease today, and the variety of medicinal drugs available can only slow its progression. Some of these drugs might be more effective if the disease could

be diagnosed earlier; by the time most diagnoses are made today, over 70 percent of the brain's cells have been impaired. In recent years, scientists have acquired much greater knowledge about the molecular processes affecting the disease's development, which has sparked a more active search for methods to slow down or arrest these processes. About 50 new drugs are now being tested clinically. A fifth of them have reached the final stage of testing on a large sample of Alzheimer's patients, after which they will require the approval of the U.S. Food and Drug Administration (FDA). The hope is that one method, or a combination of methods, will prove capable of arresting the Alzhermer's development. The following is a very brief overview of treatment directions and current research, with special emphasis on Aβ:

Improving nerve functioning—preventing the breakdown of acetylcholine

As part of the aging process, the brain loses nerve cells that produce acetylcholine. Alzheimer's disease accelerates this process in the hippocampus and cortex. The medication that has thus far received FDA approval works to stabilize the acetylcholine by inhibiting the activity of proteins that cause it to break up. There is a long list of such drugs, some of which are already second and third generation.

Anti-inflammatory drugs

Some drugs have proven successful in inhibiting Alzheimer's-related inflammation caused by microglia cells, which operate within the central nervous system's immune mechanism. Corticosteroids (steroid hormones produced by the adrenaline gland in the kidneys) such as prednisone are available for this purpose; however, nonsteroidal anti-inflammatory drug (NSAIDs) such as naproxen, indomethacin, ibuprofen, and COX-2 inhibitors are far safer because they work indirectly to reduce the activity of microglia cells. Rheumatoid arthritis sufferers treated regularly with high doses of NSAIDs are less likely, on average, to develop Alzheimer's and experience less cognitive impairment as they age.

Lessening oxidative stress

Melatonin, familiar to most of us as a drug for countering the effects of jetlag, is a natural hormone created and secreted by the pineal gland in the brain. This gland diminishes in size over the years, producing less melatonin and accelerating the aging process.

Melatonin is the most effective of all natural antioxidants and the only one capable of penetrating every cell in the body and crossing the blood-brain barrier (BBB), cell membranes and organelles. Its greatest concentration is in the mitochondrials. Alzheimer's patients are found to have melatonin levels five times lower than healthy individuals of the same age. This is an invitation for free radicals produced in the mitochondrials to damage them and set off a chain of events leading to the neuron-pathological changes that characterize Alzheimer's. Melatonin has been shown to improve the functioning of Alzheimer's patients and slow down their decline significantly.

Natural substances

Estrogen

A number of research studies have concluded that women who received estrogen hormone treatment during menopause have lower rates of Alzheimer's disease generally than women who were not so treated. Estrogen increases acetylcholine activity, encourages cell growth and cell interaction, improves blood flow to the brain, and (under laboratory conditions, at least) appears to inhibit the toxic effects of Aβ. Estrogens can even reduce inflammation and oxidative damage. All in all, an excellent treatment for Alzheimer's—except for one catch: estrogen increases the risk of breast cancer and stroke.

Ginkgo bilboa

This antioxidant, whose source is the Chinese Ginkgo, or "Maidenhair" tree, is usually sold as a botanical food supplement and aid to memory and concentration. A comparative study found that one of its effects is to improve learning and memory to some extent. Since it also raises the risk of stroke, its use for combating disease is debatable.

Reducing the amount of Aβ in the brain

Amyloid beta is produced normally and routinely in healthy individuals as well, but its creation, breakdown, and transfer from one site in the body to another is very strictly controlled. An accumulation of Aβ in the brain can be the result of three processes: an accelerated breakdown of APP, a delayed breakdown of Aβ, and transport disturbances between the brain and the blood. Researchers attempt to intervene in these processes in their efforts to develop medication for Alzheimer's.

Minimizing Aβ toxicity

After APP is cut, the Aβ created undergoes several structural processes. At first it is pliable and formless, and, as such, is also soluble and non-toxic. It becomes toxic when it folds to form a beta surface. Beta surfaces are attracted to each other to form fibers that intertwine, much like threads that work themselves into a thick rope.

Today, the world of science recognizes about 20 different amyloid diseases that share the structural mechanism described here. In each one of these diseases—among them type 2 diabetes, rheumatoid arthritis, and atherosclerosis—a relatively short protein chain is the building block for the creation of long fiber-like structures and, as such, it causes damage to its environment. While scientists have only just begun to understand how these fibers are created, it is clear that if their development can be halted early on, or if the process can be reversed, the toxic effects of this building block can be minimized—even if the process is already under way. Since amyloid diseases share the same basic mechanism, we can postulate that the discovery of a successful treatment for Alzheimer's will be good news for those suffering from other amyloid diseases.