What Goes Wrong in Alzheimer's Disease

By the time British author Iris Murdoch felt that she was "sailing into the darkness," Alzheimer's disease had long been at work on her brain.

At one time, Murdoch could compose books — in their entirety — in her mind. But in a handful of years, the disease transformed her brilliant intellect to that of "a very nice 3 year old," according to her husband, John Bayley.

Her dark descent, captured in the recent movie Iris based on Bayley's books, illustrates the plight of some 4.5 million Americans, a number expected to more than triple by 2050.

What goes so terribly wrong in the brain of an Alzheimer's patient?

This much we know. In Alzheimer's disease, lesions — called tangles and plaques — pepper the brain's memory center like buckshot. The tangles clog nerve cells with gummed up cytoskeletal proteins. Plaques — accumulations of a toxic snippet of a protein — pack up the spaces between cells. And brain tissue gradually disappears along with the victim's memories.

"You're looking at a disease that has been progressing for 30 years," said Sangram Sisodia, director of the Center for Molecular Neurobiology at the University of Chicago and a leading Alzheimer's researcher. "The plaques and tangles are the tombstones of the disease."

The search for an exact cause has led scientists to suspect that a toxic byproduct of a cell protein damages and kills nerve cells in the process of forming plaques.

"Genetics points me in the direction of a molecule called a-beta and a-beta biology," Sisodia said. The UGA alumnus earned his doctorate under the direction of Gordon Patel, who is now UGA's vice president for research and associate provost.

Plaques form when a normal cell protein called APP — or amyloid precursor protein — gets cut by enzymes in the wrong spot, releasing a toxic fragment called a-beta peptide. The plaques themselves are not thought to kill brain cells; scientists suspect that a wayward form of the a-beta peptide is the culprit.

"The a-beta peptide not only accumulates in plaques but along the way it will form these little fibrils that will be free-floating in the brain," said Rudolph E. Tanzi, professor of neurology at Harvard Medical School and director of the genetics and aging research unit at Massachusetts General Hospital. "The fibrils can interact with neurons and cause problems, from blocking neural transmission to actually killing nerve cells."

Sisodia, Tanzi and many other researchers have hunted for genetic evidence by turning to families where Alzheimer's disease strikes early — in the third or fourth decade of life, sometimes even earlier.

"The pathology in individuals who inherit these genes for early-onset Alzheimer's disease and the clinical symptoms are almost indistinguishable — with some minor variations — from somebody who gets the disease in the late onset form," Sisodia said.

So far, the genetic clues support the notion that a-beta peptide production in the brain is the probable cause of Alzheimer's disease.

"The pathological cascade inside the cell revolves around the life cycle of the a-beta peptide," said Tanzi, co-author of Decoding Darkness: The Search for the Genetic Causes of Alzheimer's Disease.

The disease occurs when a person has defective genes that either make too much APP or produce enzymes that cut APP in the wrong place, releasing the "bad" a-beta. But a-beta production alone won't cause the plaques to form; a-beta has to clump together into fibrils to be toxic to nerve cells. If enzymes chop up a-beta or if a-beta is shuttled into the blood where it can be disposed of, clumping doesn't occur, Tanzi said.

"If too much a-beta is made at once and the machinery for clearing it or degrading it can't keep up, it's going to form fibrils more readily," Tanzi said. "They're going to cause neurotoxicity and eventually it's all going to manifest itself in senile plaques."

Scientists still have much to learn about this bewildering disease that kills the mind long before the body dies. Several UGA researchers are contributing to understanding Alzheimer's disease in a variety of studies. They include the following:

- Cell biologist Marcus Fechtheimer and his research team developed a system to investigate abnormal cell structures called Hirano bodies and what their role may be in Alzheimer's and other neurodegenerative diseases.
- Walter Schmidt, assistant professor of biochemistry and molecular biology, studies several enzymes in yeast that bear similarities to enzymes thought to have roles in Alzheimer's and other diseases. One of those enzymes is similar to 1-insulin or IDE — which may remove the a-beta peptide from the brain.
- Alan Przybylek's biochemistry and molecular biology lab has developed a method to produce a recombinant form of the a-beta peptide. He helped form a start-up company, rPeptide, that provides researchers around the world with molecules involved in Alzheimer's, Parkinson's and other diseases.
- William Kisaalita, associate professor of biological engineering, is developing cell-based tests, or biosensors, to screen drugs for Alzheimer's disease.
- Alvin Terry, associate professor of pharmacy, studies the long-term effects of medication on the brain, particularly medications commonly used to treat people with diseases that affect memory, like Alzheimer's disease and schizophrenia.

Illustration by Wendy LaCapra

A normal cell protein called APP (or amyloid precursor protein) is a highly essential protein in the body. But to be active, it must be secreted from cells and that involves cutting the protein in two spots. Where the cuts occur determines whether the fragments that are released help or harm a person.

1. APP extends like a rope from the cell's interior, through the cell membrane to the cell's exterior.
2. Under normal conditions, the APP protein is cut in two places: in the cell membrane (γ) and outside the cell (α) releasing the active form of the protein.
3. Less frequently, the protein is cut at a slightly different spot (β) and cuts make all the difference. Toxic fragments called a-beta (red segment from β to γ) are released that can form the amyloid plaques characteristic of Alzheimer's disease.