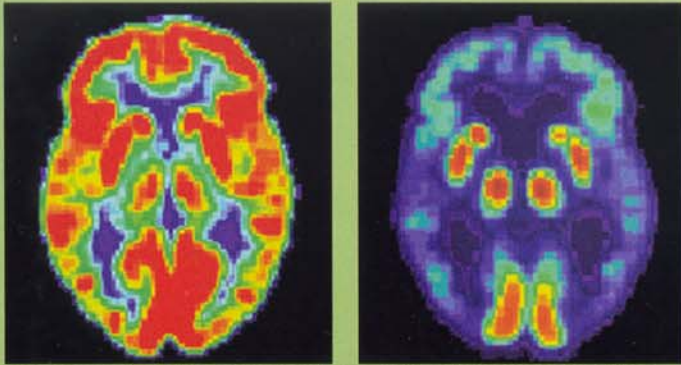


What Goes Wrong in Alzheimer's Disease



Illustrations courtesy of the Alzheimer's Disease Education and Referral Center, a service of the National Institute on Aging.

PET scans show the decline in metabolic activity in an Alzheimer's brain (right) compared to a normal brain (left).

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 — gunk 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 Gordhan 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*.

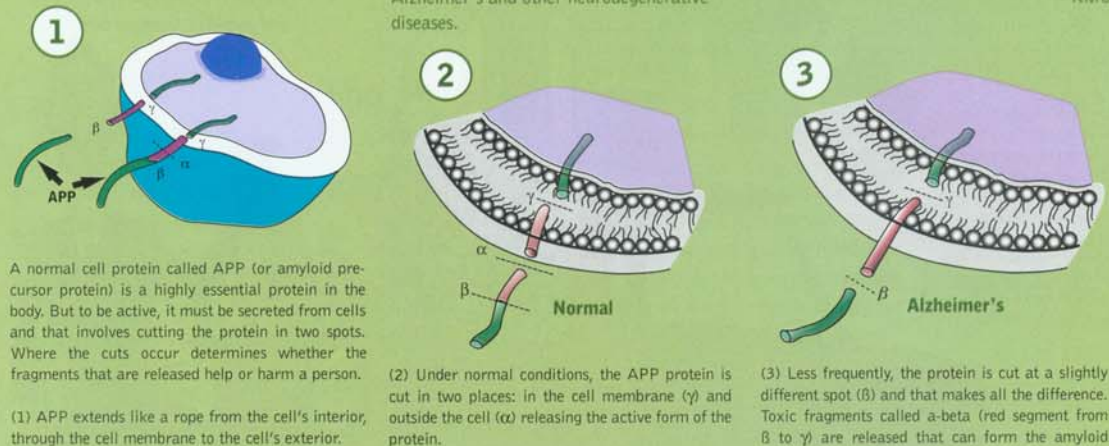


Illustration by Wendy Ginninski

• 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 insulin — or IDE — which may remove the a-beta peptide from the brain.

• Alan Przybyla'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.

— KMC