Mice Show Alzheimer Brain Plaques

Former President Ronald Reagan and as many as 4 million others in the United States suffer from Alzheimer's disease, a progressive disorder that causes impaired thinking, memory loss, and eventual death.

The cause of Alzheimer's remains unknown. No cure exists. And researchers have repeatedly failed in their efforts to produce a suitable animal model for the disease.

Until now.

Now, Ivan Lieberburg of Athena Neurosciences in South San Francisco and his colleagues have developed mice whose brains suffer damage strikingly similar to that seen in humans with Alzheimer's disease.

"This is the holy grail of Alzheimer's research," Lieberburg says. "I never expected to see this in my lifetime."

Other researchers agree that a mouse model for Alzheimer's disease would represent a significant turning point in the scientific community's search for new treatments.

"If this new model is validated by others, it will be very useful both to explore the scientific ideas and to design and test new kinds of therapeutic agents," says Leonard Berg, a neurologist at Washington University School of Medicine in St. Louis.

Until now, researchers have had to rely on test-tube models of this disorder, says Berg, who also serves as chairman of the medical and scientific advisory board of the Chicago-based Alzheimer's Association.

Lieberburg's team began its endeavor knowing that the brains of people who have died of Alzheimer's disease are strewn with plaques. These plaques — dying nerve cells surrounding a core of protein fragments called beta-amyloid — correlate with the advance of dementia.

Lieberburg's group first created genetically engineered mice that carry the human gene coding for a precursor substance to beta-amyloid. The team then demonstrated that these transgenic mice crank out the human beta-amyloid associated with Alzheimer's disease.

Finally, the researchers looked for age-related changes in the brains of the mice. "Up to 6 months of age, we really didn't see much of anything," Lieberburg says.

However, from 6 to 9 months of age the mice exhibited increasing deposits of beta-amyloid in certain regions of the brain, including the cortex, which is responsible for higher thought as well as memory.

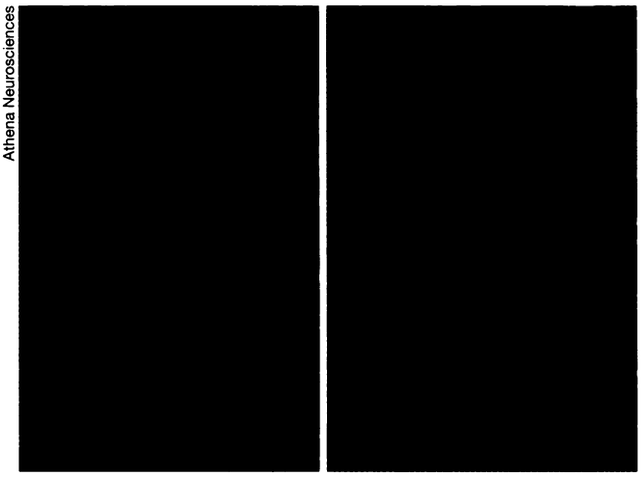
Older mice had brains so littered with these amyloid plaques that they resembled the brains of people with advanced Alzheimer's disease.

Mice that had not been genetically altered showed no plaque formation.

The research team has yet to demonstrate that the genetically altered mice show any symptoms of dementia — unlike people, mice cannot forget where they've left their car keys. Still, the researchers hope to prove impairment in these animals in other ways, perhaps in their ability to find their way through a maze, Lieberburg says.

This mouse model may help scientists design a drug to block the plaque formation observed in Alzheimer's disease. Yet even with an animal model, researchers say it may take many years to find a promising drug that works in humans. — *K. Fackelmann*

Athena Neurosciences



The mouse brain (left) shows plaque deposition, as does the brain of a person with Alzheimer's disease (right). In both photos, nerve cells are pictured in green. Red areas represent plaques with their cores of beta-amyloid, a small protein thought to kill neurons. Yellow depicts areas of overlap.

Pathfinding made easier by chemical waves

Computers can beat humans at many tasks, but they often do it by brute force. To find the quickest route through a maze, for example, a computer typically calculates every possible path and chooses the fastest. Now, researchers have found a shortcut to this computation: Just follow a chemical wave.

A chemical wave is a self-propagating reaction front that moves through certain kinds of media. Compared to physical waves, chemical waves have some odd properties: They move at a constant speed, skirt barriers without breaking up, and vanish at dead ends.

Oliver Steinbock *et al.*

Computer map of optimal distances made by combining 250 images of a chemical wave that began at S. The farthest points are blue; white lines mark equidistant paths.

A group led by chemist Kenneth Showalter of West Virginia University in Morgantown took advantage of these properties to find the shortest route through a maze. To make a chemical wave, they soaked a small square of polymer membrane in an acidic solution of bromate ions, malonic acid, and an iron catalyst. They cut pieces from the membrane, leaving the corridors of a maze.

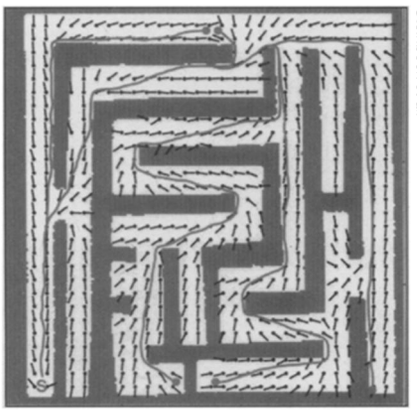
The researchers then touched a silver wire to one edge of their maze to set off a wave and took a video image of the wave front every 10 seconds. These snapshots, fed into a computer, gave them a composite image from which they derived a grid of vectors.

"You have a whole lot of information in this grid," Showalter says. A computer might have to do thousands of trial-and-error calculations to find the shortest path in a grid that size, he explains. But using the vector field from the chemical wave, "you can pick any point at random, and you automatically know how to get back to the starting point just by following the vector flow."

"You could call it a parallel approach," Showalter adds. "You do

many things at once."

The team also simulated chemical waves in mazes on a computer. This approach to solving mazes could have practical applications, says Showalter, who describes the work with his colleagues Oliver Steinbock and Agota Toth in the Feb. 10 SCIENCE. For example, it could help a robot in a huge warehouse with hundreds of rows of shelves find the best path to ferry a package to the loading dock.



Steinbock *et al.*

Vector field and five paths to point S calculated from computer map on p. 84.

Showalter also speculates that pathfinding might play a role in the excitable media of living systems, such as the cerebral cortex.

The brain's efficiency seems to depend on the arrangement of neuronal pathways, he notes. "[Could] the fact that the cortex is an excitable medium [be] connected to optimization of these neuronal pathways?" Showalter asks. "You have to wonder." *— J. Kaiser*

Fossil hints at hominids' European stall

Excavations at an archaeological site in the nation of Georgia have yielded a fossil jaw that, according to its discoverers, represents the earliest known evidence of human ancestors in that region of Asia — and perhaps anywhere outside Africa.

The well-preserved lower jaw, complete with all of its teeth, belonged to a *Homo erectus* individual who lived between about 1.8 million and 1.6 million years ago, assert Leo Gabunia and A. Vekua, both anthropologists at the Georgian Academy of Sciences in Tblisi.

If this age estimate holds up, it suggests that a substantial delay occurred before human ancestors moved from western Asia into Europe. Prior studies place the human occupation of Europe at no earlier than 500,000 years ago (SN: 10/8/94, p.235).

"[This] suggests that humans either waited outside the 'gates to Europe' for more than 1 million years or inhabited the subcontinent at a very low density during that interval," Gabunia and Vekua conclude in the Feb. 9 NATURE.

The new fossil came to light at Dmanisi, a settlement that achieved regional prominence between 1,200 and 800 years ago. After excavations began in 1981, researchers noted that the bones of now-extinct animals dot the walls of deep pits once used for grain storage. In 1991, the exploration of one such pit turned up this jaw of a hominid, or member of the human evolutionary family.

The specimen contains small teeth attached to relatively thick bone, the scientists say. The jaw shows several similarities to *H. erectus* fossils from Africa as well as to some Chinese finds, they contend.

A basalt deposit adjacent to the hominid-bearing soil dates to 1.8 million years ago. This estimate relies on a comparison of the amount of radioactive potassium in the basalt to the amount of radioactive argon, into which potassium decays. Measurements of magnetic reversals in the soil and analysis of associated animal bones further narrowed the age range for the ancient jaw.

Some scientists argue that Indonesian *H. erectus* specimens are about as old as the Dmanisi jaw (SN: 3/5/94, p.150).

Researchers don't know why human ancestors in western Asia waited for roughly a million years before trekking west, write David Dean of Case Western Reserve University in Cleveland and Eric Delson of the City University of New York in an accompanying comment.

Frigid temperatures and dangerous carnivores in Europe may have kept *H. erectus* at bay until the species developed stone weapons and social systems sufficient for survival under such inhospitable conditions, they propose.

Bernard Wood of the University of Liverpool in England, who has briefly examined a cast of the Dmanisi jaw, says it may belong to *H. erectus, H. ergaster* (which he considers the direct ancestor of modern humans), or archaic *H. sapiens.* *— B. Bower*

New evidence of neutrino oscillations

Of the fundamental particles of matter, neutrinos are among the most elusive, though theorists postulate that these particles are plentiful in the universe. Originally thought to have no mass, neutrinos barely interact with other forms of matter, making them extremely difficult to detect.

Now, a 2-year experiment at the Los Alamos (N.M.) National Laboratory has produced evidence supporting the idea that neutrinos actually have a mass, albeit a small one. This finding has important implications for cosmology, because it allows neutrinos to account for much of the mass in the universe.

D. Hywel White of Los Alamos and his coworkers at 11 other institutions announced their preliminary findings last week and plan to submit them to PHYSICAL REVIEW LETTERS.

According to the standard model of particle physics, neutrinos come in three varieties: the electron neutrino, muon neutrino, and tau neutrino, along with their antimatter counterparts. The theory says that these particles have no mass. If they do have a mass, however, neutrinos of one type would be able to transform themselves into neutrinos of another type through a process known as oscillation.

The Los Alamos experiment involved the liquid scintillator neutrino detector (LSND), which is particularly sensitive to certain neutrino transformations — if they occur. The researchers used a particle accelerator to fire high-energy protons into water to create pions. These pions decay into muons, muon neutrinos, muon antineutrinos, and electron neutrinos, but not electron antineutrinos.

The neutrinos collide with atomic nuclei in the detector, which consists of a vat of mineral oil surrounded by an array of photodetectors. The collisions create electrons and other charged particles, which leave detectable trails of light in the liquid.

In two runs, the second completed last November, the team detected 29 events indicating the presence of electron antineutrinos, which normally would be absent. One explanation is that they were created from other types of neutrinos; this suggests that neutrinos have a mass.

Considering limits set by the LSND's sensitivity, the neutrino's mass appears to be at least 0.5 electronvolt. By comparison, an electron has a mass of about 511,000 electronvolts. Though small, such a neutrino mass, multiplied by the number of neutrinos in the cosmos, could contribute significantly to the universe's total mass.

At the same time, the LSND data don't necessarily rule out alternative explanations for the presence of electron antineutrinos. "With such an important result, we need more data to establish this hypothesis firmly," White says. The researchers plan to run another LSND experiment in August. *— I. Peterson*