

HEALTHY LIVING

Tests close in on the cause

Researchers isolate a culprit, 'on brink' of validating theories

BY KEN FOSKETT
Cox News Service

New drug trials for Alzheimer's disease are enrolling patients in Atlanta and other cities amid increasing optimism that a cure for the fatal brain disorder is within reach.

Closely watched by researchers, the trials are the most significant involving Alzheimer's in at least six years. Several involve vaccines that target the suspected causes of Alzheimer's and potentially even reverse its destructive progression through the brain.

Even if the trials fail, they may at least validate — or disprove — theories about what causes Alzheimer's and how it induces brain cells to die.

"This is such an exciting time," said Dr. James Lah, an Alzheimer's researcher at Emory University, speaking to some Atlanta residents about the trials. "We are on the brink of making major breakthroughs."

More than 5 million Americans have Alzheimer's, with the numbers expected to rise sharply as Americans live longer. The disease, which is not limited to the elderly, is a progressive brain disorder characterized by short-term memory loss, muddled thinking and an inability to perform complex tasks.

Emory's Alzheimer's Disease Research Center, one of 32 around the country, is enrolling patients in at least eight new trials this year.

A total of 146 trials are under way nationally, with more than half having accumulated enough data to begin evaluating how well the drugs work.

Findings may still be several years

away and Food and Drug Administration approval even further. But research horizons are typically measured in decades, not years, so the presence of so many drugs at this stage of testing is significant, said Dr. Allan Levey, the Emory center's director.

"These are the first trials that are really capitalizing on what we know about the disease," Levey said.

While optimistic, Levey and others caution that the newest trials targeting the suspected causes of Alzheimer's may fail, and they warn that they all carry risk.

Researchers were excited about a vaccine that went into clinical trial in 2001 after showing extraordinary results in mice.

The trial was abruptly halted in 2002 after 18 patients, 6 percent of those enrolled, developed encephalitis, a potentially fatal inflammation of the brain.

Treating symptoms

More than 100 years have passed since Dr. Alois Alzheimer, a German physician, first documented that a patient he'd diagnosed with worsening memory problems died with a brain profoundly altered by disease.

Yet the cause of the degeneration eluded scientists for decades.

Then in the 1970s, they learned that Alzheimer's patients had low levels of a chemical that helped brain cells communicate.

The first Alzheimer's drug, Cognex, wasn't out until 1993. It helped increase levels of the depleted chemical but had to be taken four times a day and had only modest effect.

"I used to joke that if you could remember to take it four times a day, you didn't need it," said Dr. Richard Stefanacci, director of the Health Policy Institute at the University of the Sciences in Philadelphia.

Newer drugs, while better, still only treat symptoms, making



An elderly man is screened for Alzheimer's disease with a test that involves identifying faces in photographs at Emory University in Atlanta.

PHOTOS BY JOEY IVANSCO / COX NEWS SERVICE

the brain's healthy cells work better.

The latest experimental drugs are the first to attack the suspected causes.

Protein out of balance

The most widely held theory about Alzheimer's involves a protein called beta amyloid that gets out of balance inside the brain.

Alzheimer's patients accumulate too much, either because they produce too much or because their bodies fail to clear it out.

By itself, beta amyloid is harmless.

But over time, it sticks together, clumping in solid masses called plaques.

The plaques cause brain cells to withdraw, disrupting the links to stored memories and regions of the brain that direct executive function.

Over time, the amyloid sets off a toxic chain reaction that causes brain cells to die. At death, Alzheimer's patients have typically lost 30 percent of their brain cells.

Several gene sequences increase the risk of Alzheimer's, and risk escalates with age. Someone older than 85 has a nearly 1-in-2 chance of getting Alzheimer's.

Because Americans are living longer, the number of Americans with Alzheimer's could increase from 5.1 million today to 16 million by 2050, according to the Alzheimer's Association, increasing the urgency for an effective treatment.

Avoiding side effects

Despite the aborted vaccine trial in 2002, drug companies continued to develop vaccines because they worked in mice. Researchers also reported improved memory function among the patients from the 2002 study who did not develop encephalitis.

Elan-Wyeth, a collaboration between

Elan Corp. and Wyeth Pharmaceuticals, the developers of the vaccine that triggered encephalitis, has a new compound now entering a phase III trial with more than 2,000 patients. Phase III trials test the drug's effectiveness in larger numbers of patients and is the last before FDA approval.

Synthetically engineered from a mouse antibody, the Elan-Wyeth compound is designed to drag beta amyloid into the bloodstream, where it can be chewed up like any other foreign invader.

A passive vaccine, the drug provides the patient with the antibody, rather than stimulating the patient to produce his or her own.

Merck & Co., meanwhile, has launched a phase I safety trial of an active vaccine, similar to vaccines for chickenpox and the flu, that train the body to encode its own antibodies.

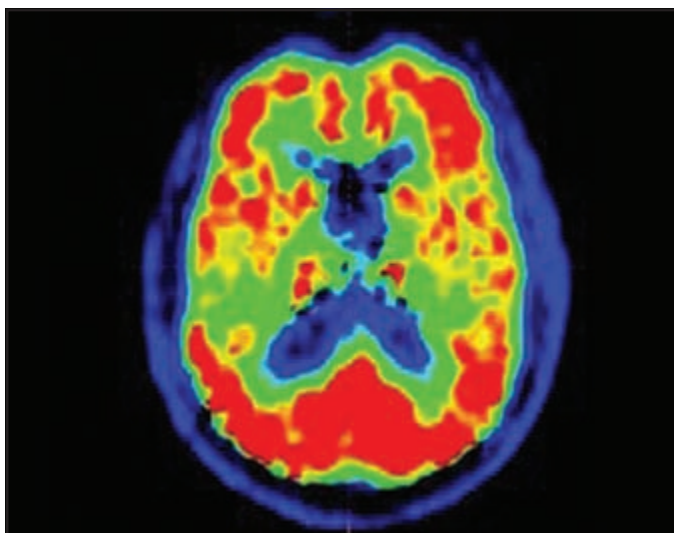
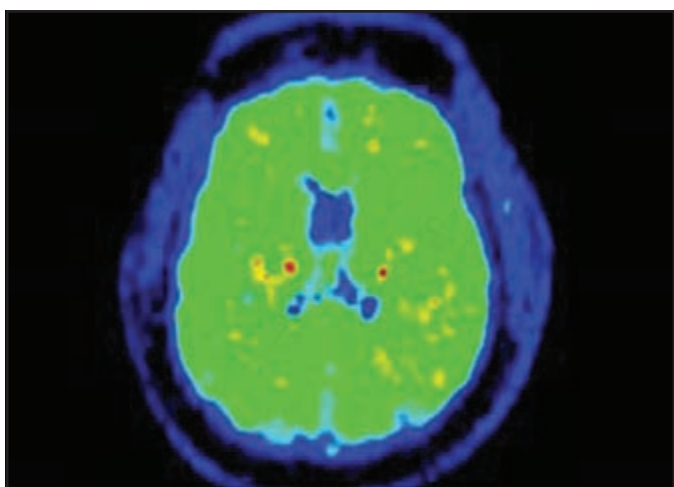
The goal of the Merck trial is to see whether the vaccine stimulates an immune response without triggering encephalitis or other side effects. The body's ability to generate immunity declines with age, so stimulating the response will be an important test of the vaccine.

Another strategy involves drugs that could disrupt the chemical reaction that makes beta amyloid.

Still another proposes to stop beta amyloid from clumping, acting like a lubricant that keeps it free-floating. In this state, the protein doesn't form the plaques that lead to cell death.

All of the trials will be critical toward validating the theory that beta amyloid is the principal culprit behind Alzheimer's, Levey said.

"If we can demonstrate that drugs and vaccines are doing what we want in reducing amyloid, but they still don't help treat patients, it tells us we have to revisit the cause of Alzheimer's disease," he said. ■



EMORY SCHOOL OF MEDICINE

Using a specially formulated imaging compound, Emory researchers can scan brains to look for deposits of beta amyloid, a protein seen in clumps of patients with Alzheimer's disease (bottom).