The tangled brain

Searching for drugs for Alzheimer's disease

BY EVELYN B. KELLY

When Alois Alzheimer peered through a microscope at slides of the brain of one of his deceased patients, he was puzzled by the clumps and tangles. Could this mass of deposits and threads have caused this woman's progressive memory loss and bizarre behavior? These observations, made in 1906, led to the identification of the baffling condition that bears his name, Alzheimer's disease (AD).

For anyone who has seen a friend or family member advance into the darkness of AD, the disease is devastating, taking both human and financial tolls. Despite great strides in recent years, its cause and mechanisms are still puzzling.

David Morgan, a professor in the department of pharmacology and therapeutics at the University of South Florida, underscores that need with frightening statistics: "By 2050, 16 million Americans could have AD, with a cost of over $300 billion. With the fastest-growing population segment being age 85 and older, there are some major economic concerns. Even without a cure, if we can delay with our drugs any of the debilitating stages for just five years, the money that would be saved could amount to over $50 million annually."

Morgan describes three generally accepted features of AD:

- Amyloid deposits of neuritic plaques made mostly of a protein called amyloid β, or Aβ. This protein is clipped from a large amyloid precursor protein (APP) by enzymes called secretases.
- Neurofibrillary tangles or malformations in nerve cells, combined with a protein called tau.
- Inflammation.

At present, no drugs target the underlying mechanisms of disease progression. Treatments in the United States are acetylcholinesterase inhibitors (AchEIs), which boost the level of acetylcholine, a neurotransmitter that dwindles in AD. The FDA has approved the following drugs for treatment of mild to moderate AD: Cognex (tacrine), which came to the market in 1993; Aricept (donepezil), which became available in 1997; Excelon (rivastigmine), which became available in April 2000; and Reminyl (galantamine), approved in February 2001. These products help some patients for a while, but they are not a cure.

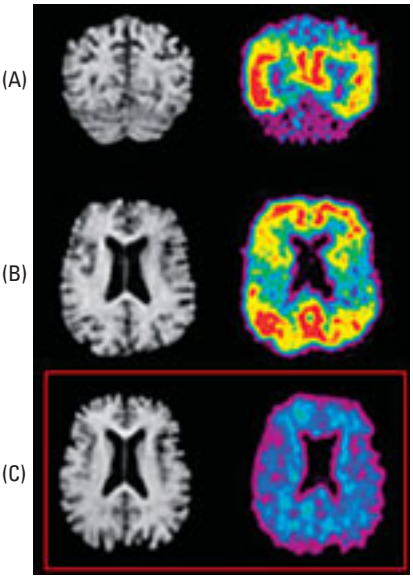


Figure 1. (A, B) Alzheimer's plaques in yellow and red, and (C) a brain without AD. (Image courtesy of the University of Pittsburgh Medical Center.)

Other drugs are in the pipeline. Takeda Pharmaceuticals has TAK-47 in clinical trials in Japan. The drug is designed to bind to the enzyme acetylcholinesterase and block its action. TAK-47 appears to survive in the brain for a long time and has a beneficial effect on brain pathways that stimulate brain energy metabolism. Phenserine, developed by Axonyx, is both an AchEI and β-amyloid precursor protein (β-APP) inhibitor. Axonyx has initiated a Phase IIB amyloid β clinical trial and a Phase III clinical trial to evaluate safety and efficacy in patients with mild to moderate AD. The dual action has the potential to improve memory and cognition and also slow the disease progression.

According to J. M. Dutton & Associates, the current worldwide neurodegenerative market is about $2.5 billion, with the AchEIs accounting for about one-third of that market. With 3.4 million patients in the United States and 2.8 million more not receiving any drug therapy, forecasters predict tremendous growth for this market. By 2005, AD therapeutics are expected to be a $3 billion-plus market. Aricept (Eisai/Pfizer) continues to be the gold standard. Pfizer reported 2003 sales of Aricept, through a licensing agreement with Eisai, of $254 million.

FDA approval given

On October 21, 2003, the FDA approved memantine, a new kind of drug and the first indicated for the moderate to severe dementia of AD. Sold as Namenda by Forest Laboratories, memantine is an *N*-methyl-D-aspartate (NMDA) antagonist. This type of drug dampens the activity of glutamate receptors.

In AD, hyperactive glutamate receptors are thought to cause neuronal death. Memantine may improve the quality of life for patients with later stages of AD, but it does not address the underlying amyloid plaques and neurofibrillary tangles.

Memantine's potential is in combination with other drugs. In a study of 404 patients, those treated with memantine and donepezil showed significant improvement in both cognitive and day-to-day function compared with patients treated with placebo and donepezil.

According to Decision Resources, Inc., the market outlook for memantine is one of exclusivity for an initial one- to two-year period. Forest has announced that after planned Phase III trials in mid-2004, it will file for the use of memantine in mild to moderate AD. Although the market is crowded in this field, memantine sales are projected to grow from $33 million this year to $350 million in 2014.

Emerging approaches

Agents that have the potential to address the underlying causes are emerging. "There are 10 or so mechanistically distinct approaches that are different from those of approved drugs," Morgan says. "Most are close to or in clinical trials, while other strategies like gene therapy are not ready for clinical testing." He predicts that one or more strategies will be effective in two and a half years.

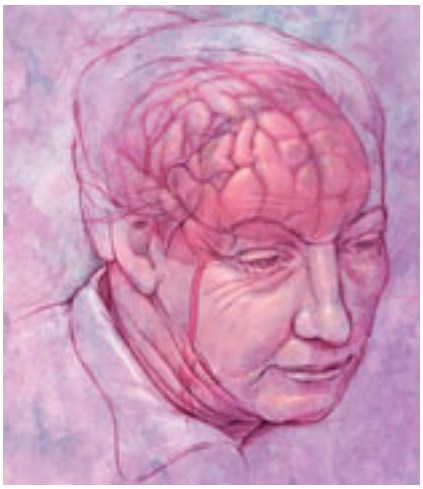
One such approach is the use of Clioquinol, a metal–protein attenuation compound, or MPAC. Ashley Bush, professor of neurology at Harvard Medical School and Massachusetts General Hospital, discovered that metals such as zinc caused strands of amyloid β to clump together. Chelation reversed the process. Bush and colleagues at the Australian company Prana Biotechnology Ltd. have published results from the first pilot study to test Clioquinol's potential. According to Bush, "The findings support a proof of concept in humans that a drug targeting metal–Aβ interaction can have a significant effect on Aβ metabolism. Clioquinol therapy is not designed to deplete bulk metals as a nonspecific chelator like EDTA might do. This drug targets a more specific protein–metal biochemical action." Bush hopes to see the drug go into Phase IIB, perhaps in the second part of 2004.

Meanwhile, several companies—including Eli Lilly, AstraZeneca, Pfizer, Elan, and Amgen—have advanced discovery programs for identifying and developing small-molecule inhibitors of β- and γ-secretases, Morgan says. Aβ-42, a 42-amino acid peptide and the mastermind behind plaque formation in the brain, has enzymes β-secretase and β-secretase as accomplices. These culprits cleave Aβ from the much larger protein APP. β-Secretase is a discrete, attractive therapeutic target for a disease-modifying therapy because it limits formation of Aβ.

Other investigators are testing anti-inflammatories. Researchers at the Mayo Clinic, the University of California at San Diego, and Myriad Pharmaceuticals tested 20 common nonsteroidal anti-inflammatory drugs (NSAIDs) and found 8 that reduced the formation of a protein implicated in AD. And Neill Graff-Radford and colleagues at the Mayo Clinic researched flurbiprofen, an NSAID drug with *S* and *R* enantiomers. Both forms lowered Aβ-42 levels in cultures of human brain cells and in mice, but *R*-flurbiprofen has fewer side effects. "This is the best thing we have in our hands today," Graff-Radford says. "We know that it's going to be reasonably safe."

Because of an apparent link between known risks for heart disease and for AD, cholesterol-lowering agents are receiving attention. The National Institute on Aging began a trial of the effects of statins (specifically, simvastatin) on AD prevention in 2003; the trial is to end in 2006. And a study released by Nymox in late February 2004 found that patients taking cholesterol-lowering statins had a 39% lower risk of getting AD. Nymox holds U.S. and global patent rights to using statins against AD.

ILLUSTRATION: ARTVILLE



At the November 2003 meeting of the Society for Neuroscience, at least two dozen presentations described current efforts to develop a vaccine for AD. This approach suffered a setback in 2002 when 6% of patients in Elan/Wyeth's Phase IIA trial of AN1792 developed encephalitis.

Cindy Lemere, assistant professor of neurology at Harvard Medical School and Brigham and Women's Hospital, Boston, works with Caribbean vervet monkeys and has reported high antibody titers and a reduction in Aβ in five vaccinated monkeys. Lemere has reported no tangles in the monkeys' brains and plans a study to assess cognition as well.

Some companies see a strategy targeting nerve growth factors (NGFs) as viable for future development. In December 2003, Neurochem, based in Montreal, announced continued positive results for Alzhemed, a fibril-dissolving amyloid deposit modulator, in open-label Phase II trials.

Meanwhile, Ebewe Pharmaceuticals of Austria is testing Cerebrolysin, which has an NGF-like activity in experimental systems. It may stimulate nerve growth and protect neurons from damage. Phase II and III clinical trials suggest that this drug improves thought processes in people with mild to moderate AD. Similarly, Sanofi-Synthélabo of France has developed xaliproden, an NGF-like molecule that has reached Phase III trials in Europe.

Neuro Therapeutics is developing AIT-082, or Neotrophin, a compound that triggers the synthesis of molecules in neurons to benefit nerve growth. In a Phase II study, the drug improved thought processes and memory.

Other companies have efforts designed to protect neurons from damage or death. Novartis, for example, is exploring the role of dihydroepiandrosterone as a nerve protectant, while Cephalon has a promising molecule, CEP-1347, designed to prevent neuron loss.

Dainippon Pharma has used thyrotropin releasing hormone to improve the levels of acetylcholine-processing enzymes in damaged areas of the brain. And Cortex Pharmaceuticals is testing Ampalex—an ampakine that modulates the AMPA receptors, a subtype of glutamate receptors—in Phase II trials. The drug increases the synaptic responses in the hippocampus and quickly crosses the blood–brain barrier. A possible role in attacking plaques and tau tangles is also under investigation.

According to Andrea Witt, an analyst with the market research firm Decision Resources, the market for the mild to moderate patient population will continue to be crowded. However, memantine and other AchEIs will probably still sell well because of the possibilities for combination therapy. But other approaches and agents that modify the disease process could emerge and alter the landscape of AD management. And new diagnostic techniques also could shift emphasis toward treating the disease in its earliest stages.

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