Continued from previous page

thetic form of the 42–amino acid Aβ peptide.

Phase I human studies indicated the compound was safe, but the phase II placebo-controlled study in 372 patients proved otherwise: 18 of the subjects (5%) developed encephalitis after just two of the six planned injections. Researchers postulated that the encephalitis was the result of T-cell hyperactivation, probably because the long amino acid string stimulated T-cell epitopes.

Although the study was halted early, investigators continued to follow the subjects. In the intervening years, some have died (all of causes unrelated to any adverse events of the vaccine), and autopsy reports from five have provided some striking findings, said Dr. Gilman, who served as an independent consultant and chair of the safety monitoring committee for the interrupted trial.

"We have as-yet unpublished autopsy reports that are absolutely dynamite—just staggering," Dr. Gilman said in an interview. "They show large volumes of the brain where Aβ had been deposited and was removed. We can tell this from the tracks that remain. The tissue underneath showed a lot of loss of nerve cells, but there was no scarring."

The most compelling evidence was seen in a subject who died just a few months after receiving his final injection of AN-1792. "Not only could we see the inflammatory cells that had removed the plaques, but we caught them in the act. The microglia had been activated and were working away," clearing the lesion, Dr. Gilman said.

This is "wonderful evidence" that the vaccine did what it was intended to do—remove Aβ plaques via active immunization. But the immune response occurred in only about 20% of the subjects, many of whom exhibited another odd side effect—decreased brain volume. After 12 months, responders' brains had shrunk 1.5 times more than those of nonresponders, while their ventricles had enlarged about twice as much.

"Our initial hypothesis that there would be stabilization of brain volume was wrong," Dr. Gilman said, "but we really don't know why. Our best guess at this point is that the shrinkage was related to fluid loss that accompanied the removal of the Aβ."

Dr. Gilman said the volume loss didn't correlate with cognitive function. The responders had better composite scores on memory tests than did the nonresponders or those in the placebo group—but just barely.

Most of the cognitive tests, including the MMSE, showed no differences among the groups—all three continued to decline equally. But the composite score from a neuropsychological test battery showed "less worsening" in the responder group than in the placebo group, as the responders had the best scores on the composite memory tests.

Dr. Gilman said he was encouraged, pointing out that the trial's main end points were safety and immunogenicity, not cognition. And, he said, since the study was stopped early, it's hard to predict what the cognition results could have been.

"We have proof of concept that the idea was correct, and we have information indicating that memory was relatively preserved," he said. "That's enough for the research to continue." ■

Some Researchers Don't Buy the Amyloid β Theory

Drug companies are betting big on immunotherapeutic approaches to Alzheimer's disease, but the theory behind the proposed treatment—that getting rid of amyloid plaques will slow or halt the disease—is by no means universally accepted among researchers.

"There are a few of us who don't worship at the Church of the Holy Amyloid," Mark A. Smith, Ph.D., professor of pathology at Case Western Reserve University, Cleveland, said in an interview. "There is a thought that the plaques are a response to disease, rather than the cause of the disease, and that they could even be performing some kind of protective function. It's certainly a less sexy theory, but it's out there" (Neurobiol. Aging 2001;22:131-46).

An increasing body of evidence supports this alternate theory (Ann. N.Y. Acad. Sci. 2004;1019:1-4), said Dr. Smith. Although amyloid plaques are a diagnostic hallmark of Alzheimer's disease, they do not uniquely occur in Alzheimer's patients—a fact that has puzzled researchers for years. The plaques also occur in the brains of many of the cognitively normal elderly and occasionally in the brains of cognitively normal middle-aged people.

Additionally, he said, both human and animal studies have shown that amyloid beta (Aβ) accumulates in the brain following head injury; about 30% of head injury patients have Aβ deposits. The precursor protein of Aβ appears to be part of the acute reaction to neuronal injury.

"The deposition of Aβ in the brain appears to be the body's attempt to compensate for whatever primary insult causes Alzheimer's," Dr. Smith said. "We don't know what that insult could be; oxidative stress related to aging, ischemia, or even hypoglycemia could be factors."

Animal studies of Aβ have reached some tantalizing conclusions about the protein's effect on neurons, he said. Animal brains injected with Aβ don't show any cognitive decline, and neurons can be cultured on top of the plaques. The protein has been shown to have antioxidant properties and protects neurons from death after injection of saline or iron.

His colleague, George Perry, Ph.D., also a professor of pathology at Case Western, supports this view and is a partner in this area of research.

One of Dr. Smith's former trainees, Glenda M. Bishop, Ph.D., holds that the plaques are both neurotoxic and neuroprotective. The weblike fibrillar structures act as bioflocculants, she said, or sinks that trap toxins, especially metal ions, and limit their potential to damage neurons. Supporting this thesis is the fact that amyloid plaques contain elevated levels of iron, copper, and zinc (Neurobiol. Aging 2002;23:1051-72).

Dr. Bishop of Monash University, Victoria, Australia, injected rat brains with human Aβ mixed with iron, copper, and zinc (Brain Pathol. 2004;14:448-52). The zinc-Aβ mixture proved more neurotoxic than zinc alone, but the other mixtures were benign. "We observed that when iron or copper were combined with Aβ, the neurotoxicity of these metals was substantially reduced, suggesting that Aβ may help to limit the toxicity of metal ions, thereby assisting the antioxidant defense of the brain," she said.

If the plaques do have a protective function, Dr. Smith said, removing them by immunotherapy could have unforeseen negative consequences. "The question of whether removing plaques will be beneficial is clouded by two major issues. First, if, as I propose, amyloid is a protective response to disease, then removal of amyloid will likely exacerbate the disease. Second, it is unclear what happens to oligomeric, soluble amyloid following vaccination."

Some researchers think soluble Aβ may be the key player in Alzheimer's, while the fibrillar plaques are innocuous bystanders. The culprits in this scenario are groups of aggregated, soluble Aβ proteins called amyloid-derived diffusible ligands (ADDLs). William L. Klein, Ph.D., of Northwestern University, Chicago, has shown that brains with Alzheimer's disease contain 70 times the ADDLs of normal brains (Proc. Natl. Acad. Sci. USA 2003;100:10417-22).

Both naturally occurring and synthetic ADDLs appear to be neurotoxic, binding to the dendritic surfaces of hippocampal neurons. This causes failure of long-term potentiation, "a form of synaptic information storage well-known as a paradigm for memory mechanisms," Dr. Klein wrote. A 2004 study indicated that anti-ADDL antibodies applied to brain sections with Alzheimer's disease resulted in diffuse staining around neuronal cell bodies, suggesting a dendritic pattern (J. Neurosci. 2004;24:10191-200).

ADDLs may help explain the poor correlation between amyloid plaques and cognitive deficits, and may provide yet another target for immunotherapy, Dr. Klein suggested in the paper. "If antibodies can be developed that uniquely target oligomers, it would raise the exciting possibility that human memory function in Alzheimer's could be preserved safely and, in some circumstances, perhaps even restored."

Dr. Klein is cofounder of Acumen Pharmaceuticals; he said in an interview that his company is working with Merck to develop a monoclonal anti-ADDL antibody for passive immunotherapy. Merck did not comment for this story; however, a press statement on the Acumen Pharmaceuticals Web site said that animal trials are scheduled to confirm benefits of this therapeutic strategy in transgenic mice.

Sleep Apnea May Be Key to Apo E4 and Alzheimer's Link

BY BRUCE JANCIN
Denver Bureau

DENVER — The well-documented association between the apolipoprotein E4 allele and development of cognitive decline and Alzheimer's disease may be mediated at least in part by obstructive sleep apnea, Ruth O'Hara, Ph.D., said at the annual meeting of the Associated Professional Sleep Societies.

This is an exciting possibility, because although there are no therapies to delay the onset of dementia, continuous positive airway pressure (CPAP) offers a highly effective treatment for obstructive sleep apnea. It may be that identifying and treating this disorder in apo E4–positive patients could delay or even prevent the onset of cognitive decline and Alzheimer's dementia, said Dr. O'Hara of Stanford (Calif.) University.

She presented a cross-sectional study of 36 community-dwelling nondemented older adults—mean age 70 years—half of whom possessed the apo E4 allele. All were assessed for cognitive performance status by the Mini-Mental State Examination and Rey Auditory Verbal Learning Test. The presence and severity of obstructive sleep apnea were assessed using home ventilatory polygraphy, she said. The most striking study finding was that although there was no difference in cognitive function between the apo E4–positive and –negative groups overall, apo E4–positive individuals with sleep apnea as defined by a higher apnea/hypopnea index had lower memory scores as reflected by worse performance on the delayed recall and short-term recall components of the Rey test. The higher an apo E4–positive subject's apnea/hypopnea index, the lower their memory scores. In contrast, the apnea/hypopnea index was unrelated to memory function in individuals who did not carry the apo E4 allele. Daytime sleepiness was unrelated to cognitive performance in either group.

Dr. O'Hara observed that it's impossible to tell from a cross-sectional study such as this whether sleep apnea is mediating the effect of the apo E4 allele as a risk factor for development of cognitive decline and Alzheimer's disease. That's a question that can be addressed only in a longitudinal study. On the strength of the provocative cross-sectional study findings, the National Institute of Mental Health has granted funding for Dr. O'Hara and coworkers to conduct a 150-subject prospective study. ■