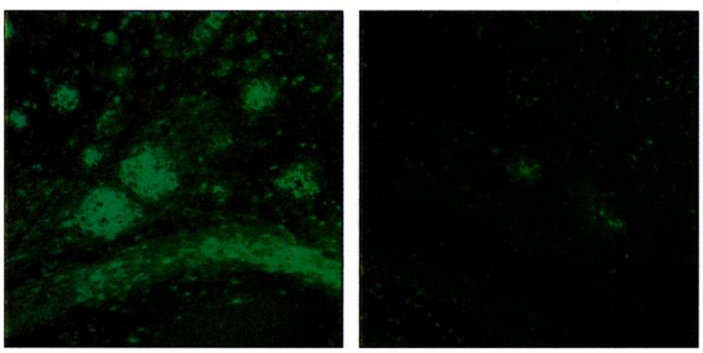
ALZHEIMER'S CONGRESS

Further Progress on a β-Amyloid Vaccine

WASHINGTON, D.C.—An experimental vaccine that can reverse Alzheimer's-like symptoms in mice is holding up under continued testing. The treatment appears to improve mental functioning in mice, and despite earlier concerns, the vaccine is well tolerated by a variety of animals—possibly including humans. Excitement was palpable at last week's World Alzheimer Congress 2000, but researchers caution against undue optimism.

"We don't want to overpromise," says Zaven Khachaturian, former director of Alzheimer's research at the National Institutes of Health and currently a consultant to the Alzheimer's Association and other organizations. He and others point out that experimental therapies that work in mice have often failed to pan out when tested in humans. And so far, there is no evidence that the vaccine can improve the cognitive functioning of Alzheimer's patients.



Gumming up the works. Amyloid deposits (green) proliferate in the brains of mutant mice *(left)* unless they have been vaccinated *(right)*.

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The vaccine being tested contains a small protein called β amyloid (Aβ). This protein forms abnormal deposits, or "plaques," in the brains of people with Alzheimer's disease. Many Alzheimer's researchers think that deposition of Aβ, which is neurotoxic, causes the patients' loss of mental function by killing their brain neurons. Aβ vaccination is supposed to prevent that mental deterioration by stimulating the body's immune system to clean up plaques and prevent further Aβ deposits.

The first evidence that such a vaccine could work came last year from Dale Schenk and his colleagues at Elan Pharmaceuticals in South San Francisco. Because of Aβ's apparent role in Alzheimer's, several research teams have tried to reproduce the disease in mice by genetically engineering the animals so that they develop the telltale amyloid plaques. In some cases, the altered mice also show learning and memory problems. When the Elan team immunized one strain of Alzheimer's-model mice with Aβ, they found that animals vaccinated before plaque deposition begins developed fewer plaques than their untreated littermates. And in older mice, vaccination actually caused Alzheimer's-like plaques to disappear (*Science*, 9 July 1999, p. 175). The finding "surprised just about everyone in the field," says Bruce Yankner of Harvard Medical School in Boston.

There were worries, though, that injecting animals with a protein found in the body could trigger an autoimmune response. Now Schenk says his team has more evidence that the vaccine is safe: Vaccinated guinea pigs, rabbits, monkeys, and other animals show no indications of autoimmunity or other toxic reactions.

The researchers have also begun to test the vaccine for safety in people with mild to moderate Alzheimer's disease and reported encouraging preliminary results. But this phase I clinical trial involves just 24 patients, who received only one dose of the vaccine. Any likely vaccine strategy would require booster shots, says neurologist Stephen DeKosky of the University of Pittsburgh, who expects more relevant safety data to emerge from an ongoing British trial in which volunteers are receiving a dose of the vaccine every 2 months for a year.

Neither safety trial will test whether the vaccine actually improves the patients' conditions. But particularly in the U.K. trial, researchers hope to determine whether the vaccine at least stimulates production of antibodies to Aβ, a critical first step.

There is some evidence of immune involvement in Alzheimer's. At the congress, Yansheng Du of Indiana University Medical School and Eli Lilly and Co., both in Indianapolis, reported that people naturally carry antibodies to Aβ in their cerebrospinal fluid. What's more, Du's unpublished data show that people with Alzheimer's had 30% fewer antibodies than age-matched healthy controls. This could mean, he suggests, that people who develop Alzheimer's have an immune system deficit that allows Aβ to build up. Alternatively, the antibodies might stick to amyloid plaques in the brains of people with Alzheimer's disease, leaving fewer circulating in the cerebrospinal fluid.

Although it will be at least several years before there are data on a vaccine's efficacy in humans, animal studies are encouraging. Two independent teams reported at the conference that Aβ vaccination seems to preserve memory and learning ability in plaque-producing mice.

In one study, Christopher Janus and his colleagues at the University of Toronto compared the performance of vaccinated and control animals in the Morris water maze. This maze is a standard memory test in which animals are supposed to learn the location of a submerged platform in a water bath. The researchers found that even weeks after Alzheimer's-like memory disorders were apparent in nontreated littermates, immunized mice performed as well as mice who weren't engineered to develop amyloid plaques.

In a similar study, David Morgan and colleagues at the University of South Florida in Tampa modified the water maze so that they could count how many wrong turns the animals took when searching for the hidden platform. After training the mice to find the platform, the researchers waited 30 minutes—to get a measure of short-term memory—and let them try again. Mice engineered to have amyloid plaques "haven't a clue" about how to find the platform, says Morgan. But vaccinated mice were "nearly flawless." They remembered the location of the platform as well as control mice that lacked the genes that cause amyloid plaque deposition did.

Researchers haven't agreed yet on how the vaccine works. Schenk's earlier study showed that mice injected with Aβ develop antibodies to the protein that can move from the blood into the brain. There, they apparently trigger scavenger cells called microglia, which devour amyloid deposits. Subsequent studies with plaque-infested neurons in culture support that idea, Schenk says. But the South Florida team found that Aβ vaccination had little effect on plaque deposition in their animals, a finding that suggests some other, as yet unknown mechanism. Whatever the mechanism, says DeKosky, "the fact that mice are helped behaviorally gives a big boost to the discussion of the potential utility of this technique" in humans.

–LAURA HELMUTH

ALZHEIMER'S CONGRESS

Drug Shows Promise For Advanced Disease

Although the β-amyloid vaccine now being explored as a potential Alzheimer's therapy attracted the bulk of the attention at the World Alzheimer Congress 2000 (see story above), another, more conventional, drug is showing promise in clinical trials. Neuropsychiatrist Barry Reisberg of New York University School of Medicine reported at the "hot topics" session of the congress that the drug memantine significantly slowed the