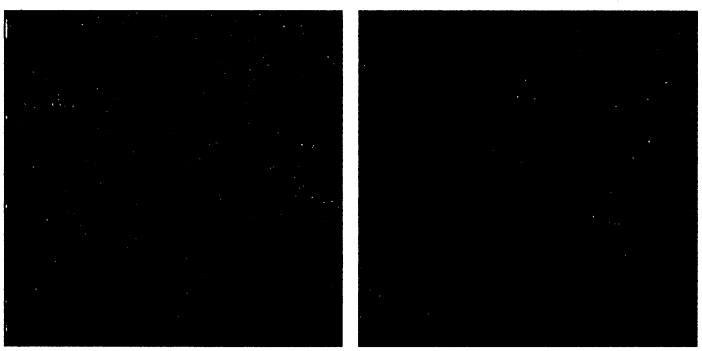
ALZHEIMER'S CONGRESS

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)*.

CREDIT: ELAN PHARMACEUTICALS

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

progression of Alzheimer's symptoms in patients with moderately severe disease.

Neil Buckholtz, who manages the Alzheimer's drug development program at the National Institute on Aging in Bethesda, Maryland, says the results are interesting because "there's nothing else I know of that's worked for that population." What's more, he notes, the work suggests a new strategy for combating Alzheimer's.

The only other Alzheimer's drugs currently approved in the United States, which are directed at mild to moderate disease, act by bolstering the function of a group of neurons that are lost in the patients' brains, contributing to their mental decline. These neurons use the chemical acetylcholine to transmit their signals. In contrast, memantine turns down the activity of the so-called NMDA receptor, which responds to the neurotransmitter glutamate and whose overactivity may lead to neuronal damage in Alzheimer's.

In Germany, memantine has been approved for treating dementias for 10 years, but the study described by Reisberg—a phase III trial designed to test the drug's efficacy—is the first conducted in the United States. It included 252 Alzheimer's patients, who were treated at 32 clinical centers throughout the country. All had reached the stage when they begin to lose the ability to perform such basic daily functions as dressing and bathing and become incontinent. At the end of this stage, Reisberg says, family caregivers often find that they have to institutionalize the patients.

For the trial, the patients were divided into two groups, one of which was given memantine while the other received an inactive placebo. A variety of behavioral and intellectual assessments showed that all the patients declined over the 28-week course of the trial, but the decline was significantly slower in those taking the drug. "There was less deterioration. That makes a big difference in the burden of care," Reisberg says. He also notes that memantine seems to be well tolerated, causing few, if any, side effects. "Manipulation of the NMDA receptor system seems to be a promising target for treating Alzheimer's disease," Reisberg concludes.

Recent clinical trials in Europe, including one reported in the February 1999 issue of the *International Journal of Geriatric Psychiatry* by researchers in Latvia and at Sweden's Karolinska Institute, also bolster the case that memantine may be effective for slowing progression of dementias. Buoyed by these results, Merz & Co. of Frankfurt, Germany, which produces the drug, has entered into a partnership with Forrest Labs of New York to pursue plans for marketing memantine in this country—provided the U.S. Food and Drug Administration approves it.

–JEAN MARX

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ANIMAL RESEARCH

Activists Win Big on Rodent, Bird Rules

Animal-rights activists may have landed a knockout blow in their decade-old fight to force the U.S. government to regulate the use of laboratory mice, rats, and birds. Some research groups worry that the impact could send academic and industrial labs reeling.

A federal judge last month ruled that the activists have the legal right to challenge U.S. Department of Agriculture (USDA) rules that exempt the vast majority of research animals from federal regulation. Although the department has yet to respond, observers say that the ruling almost guarantees that the agency will extend regulations governing animal handling and housing to thousands of academic and industry laboratories that work with rodents and birds. Those new rules, say animal-care experts, could impose costly new requirements on labs that don't meet standards set by the private Association for Assessment and Accreditation of Laboratory Animal Care (AAALAC). And even AAALAC-accredited institutions worry that USDA might design its rules in ways that would require new equipment and record keeping.

Rat rules. Researchers using birds and rodents, such as this rat, could face increased regulation.

The lawsuit was filed last year by a coalition led by the Alternatives Research & Development Foundation (ARDF) of Eden Prairie, Minnesota (*Science*, 5 February 1999, p. 767). It seeks to reverse a 1972 USDA decision to leave mice, rats, and birds—which account for more than 95% of all research animals—off a list of laboratory animals regulated under the 1966 Animal Welfare Act (AWA). USDA has claimed discretion to decide which animals are exempt from regulations that require researchers to open their facilities to annual surprise inspections and to consider alternatives when designing experiments.

Animal-rights groups won an earlier round when a federal court ruled in 1994 that USDA's claim was "strained and unlikely." But an appeals court made that decision moot by ruling that the groups had no legal "standing" to sue because they couldn't demonstrate that their members were directly harmed by the regulations.

ARDF took a different tack. One of the parties to the case was Kristine Gauz, an undergraduate psychology student at Beaver College in Glenside, Pennsylvania, who claimed to have suffered "aesthetic and emotional injury" from working with laboratory rats that she says received inadequate housing and veterinary care. In a 21 June ruling, U.S. District Judge Ellen Segal Huvelle concluded that Gauz has standing. "A researcher who witnesses the mistreatment of rats in her lab must have standing," Huvelle wrote, adding that USDA does not have "unreviewable discretion to exclude birds, rats, and mice from the AWA's protection."

USDA officials won't comment on the litigation, but agency sources say they expect Secretary Dan Glickman to decide within a month whether to throw in the towel. The betting is that he'll try to negotiate a timetable for phasing in regulation of the animals. "I'd be surprised if they shed any more blood on this," says John Miller, executive director for AAALAC in Rockville, Maryland. "It is clear to everyone that USDA cannot possibly win," crows ARDF chief John McArdle.

Writing and implementing any new rules could take years, however. And there is also the question of money. Miller predicts that the added oversight of thousands of small colleges, start-up biotech firms, and backyard bird breeders might require doubling USDA's current $10 million animal-care budget and staff of 70 inspectors.

Congress may be amenable to such a request. Last year, a coalition of animal-rights and animal-care groups won a $1 million increase for USDA's inspection budget, and this year they are closing in on a $2 million boost. The need for more funds, Miller notes, unites "the otherwise warring factions."

–DAVID MALAKOFF