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AARP Bulletin

Closing In on Alzheimer's

Finally, new drugs offer real hope for reversing the disease.

By Barbara Basler
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This month, scientists are expected to announce final test results for the first in a whole new generation of drugs designed to attack the underlying cause of Alzheimer's disease—medicines that offer what one expert calls "genuine, tangible, quantifiable hope" for those with mild to moderate forms of the illness.

"Within three years, it's all but certain we'll have disease-modifying drugs that fundamentally change the nature of Alzheimer's," says Sam Gandy, M.D., chair of the National Medical and Scientific Advisory Council of the Alzheimer's Association and director of the Farber Institute for Neurosciences in Philadelphia.

Neil Buckholtz, chief of the Dementias of Aging Branch at the National Institute on Aging in Bethesda, Md., adds, "We've gone from drugs that help for a time with the symptoms of Alzheimer's to trying to develop drugs that will actually slow down or reverse the disease itself."

Gandy says that if test results for the first new drug, Alzhemed, from Neurochem, are positive, "the Food and Drug Administration could choose to fast-track the drug and we could conceivably see it approved next year."

And if Alzhemed fails to significantly slow the progress of the disease?

Scientists are still confident that one of the more than four dozen other drugs now in human trials will succeed. One of the most promising of those, Flurizan, from Myriad Genetics, should complete its tests in the next 18 months.

Experts say there is a solid basis for all this optimism: Today's drug trials are the fruit of 20 years of scientific work on Alzheimer's.

"We're now at a point where we understand enough about the molecules and mechanisms of the disease to target new therapies very, very precisely," says Douglas R. Galasko, M.D., interim director of the Alzheimer's Disease Research Center at the University of California, San Diego. "And that increases our chances for success."

This hopeful news comes as the country braces for an epidemic of Alzheimer's, the harrowing form of dementia that Americans tell pollsters they fear more than heart disease, stroke or diabetes. Today, 5.1 million people in the United States have the disease, but the greatest risk factor is age—the longer a person lives, the greater the possibility—and in just four years millions of boomers begin to turn 65. One in eight people age 65 and older now has Alzheimer's; half of those 85 and older have it.

Very few drugs make it to Phase III clinical trials, the last step before a drug goes to the FDA for approval. Today, however, nine new Alzheimer's treatments are in Phase III trials to test their effectiveness on a large number of patients. And dozens more are in smaller Phase II trials.

This next generation of drugs is designed to prevent, destroy and clean out deposits of

beta-amyloid plaque that kill the brain's nerve cells, leading to the devastating loss of memory, reason and, ultimately, life that characterizes Alzheimer's.

Researchers have repeatedly shown that when plaque is reduced in the brains of mice with Alzheimer's, the mice can solve problems and run mazes that once confounded them. And early test results for some of the new anti-amyloid drugs show they've helped Alzheimer's patients remain stable and even improve for several years.

Art Ulene, M.D., former medical reporter for the *Today* show and a board member of the AARP Foundation, says his brother, Howard, who has mild Alzheimer's, is taking part in a trial for a new drug, and the change in him has been "astonishing."

"Before the drug, he was repeating himself, his short-term memory was poor—you couldn't really hold a good, continuing conversation with him," Ulene says. "A year after he started the trial, I ... couldn't believe the change: I had gotten my brother back."

In an earlier, tantalizing study with 375 Alzheimer's patients, researchers at Elan Pharmaceuticals tested a vaccine designed to trigger an immune response that prompts the body to produce antibodies against amyloid. The vaccine had worked extremely well in mice, but the human trial was halted in 2002 when about 6 percent of the subjects developed brain inflammation.

International researchers located 159 people from the aborted study and tracked their health over four and a half years. They found that the patients who had produced antibodies were doing significantly better than those who didn't.

"The follow-up data are very encouraging," says Dale Schenk, chief scientific officer for Elan in South San Francisco. Moreover, Swiss researchers found that four patients they had tracked showed no mental decline at all. One even ran a marathon recently.

Scientists say the follow-up findings have given them a better understanding of the level of antibodies needed to produce the best results.

Now Elan, in collaboration with drug manufacturer Wyeth, is back in Phase II trials with a vaccine researchers believe is as effective as the first, but safer. Therapies that kindle immune response are so promising that scientists are testing half a dozen other vaccines in humans. Some vaccines induce the body to produce antibodies while others contain antibodies made in the lab.

"Dealing with Alzheimer's will be a bit like treating cancer in the sense that we'll need a large number of treatments," says Huntington Potter, director of the Johnnie B. Byrd Sr. Alzheimer's Center and Research Institute in Tampa, Fla. "Some people will respond well to one treatment, others to another. And we may need to use a cocktail of drugs."

The chances of hitting upon a successful therapy soon are high, experts say, because the drugs in the pipeline attack amyloid at different stages. Flurizan, for example, works to inhibit the production of amyloid while Alzhemed is believed to discourage it from forming plaque. The antibodies in the vaccines are thought to bind to amyloid and help the body eliminate it.

Experts say even if Alzhemed or another of these early anti-amyloid drugs fails, that doesn't mean the amyloid theory is wrong. It simply may mean that the drug didn't eliminate enough plaque to significantly slow or arrest the disease.

Most of the new drugs focus on amyloid. Some trials, however, are exploring the strong

correlation between heart disease and diabetes as Alzheimer's risk factors. Trials are testing cholesterol-lowering statin drugs and diabetes drugs on Alzheimer's patients. Another test is studying a drug that lowers homocystine levels—a possible risk for vascular disease—to see if lower levels slow Alzheimer's progression.

"We're not going to find one magic bullet, but I'm very optimistic we're going to see one or more of these therapeutic approaches work," says David Morgan, director of basic neuroscience research at the University of South Florida in Tampa.

Scientists are also working all out to determine the genes and other biological markers that can predict the disease before symptoms appear.

"Our best hope is to catch this disease early," says Morgan. "And if we can understand who is most at risk, we can begin treating them before it ever takes hold."

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Back to Living a Normal Life

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After almost two years on experimental Alzheimer's drug MPC-7869—later revealed to be Flurizan—Howard Ulene says his memory has improved, and while it's not perfect, life is "so much better."

"Before the drug, I would misspeak, I would forget, I'd get confused," says Ulene, 77, who was diagnosed with Alzheimer's four years ago. "I couldn't count on myself because I never knew when a blank would occur. They came so suddenly, without warning.

"This is a disease," he says, "that eats you alive."

After he learned that the University of California at Irvine—a 10-minute drive from his home—was conducting a clinical trial for a new drug, his wife, Sally, agreed to enroll him.

"Howard is a very bright, articulate man who was a successful entrepreneur," she says. "He is so bright that for a while he was very good at hiding his symptoms. But it got to the point where he was forgetting the names of his grandchildren."

As is typical of these trials, the Ulenes didn't know whether Howard was getting a drug or a placebo. But he and his family say that as the months passed, the improvement was unequivocal.

"I started to feel more like myself," Howard says. "I could tell I wasn't making the same slips."

His wife agrees. "Faced with a number of choices, like a menu, Howard gets a bit confused. But on the whole, he is doing much better," Sally says. "He's living a normal life." Howard makes his breakfast, reads newspapers, goes out to dinner with friends and plays with his grandchildren.

After 18 months, the study called for him to go off the drug for five weeks, and he immediately began to regress. He was confused, depressed. "I was really worried," Sally says. Now, Howard is back on Flurizan, which will be available to him for at least two more years.

"This drug has been wonderful, and we just hope it continues to let him hold his own

against the disease," Sally says. "We hope that for Howard and for everyone else, too."

As in any Phase III trial, however, the results aren't final until the study ends and all the data are analyzed. "We can't conclude anything for certain until then," cautions one expert.