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## 7 Ways to Save a Brain

**Current Alzheimer's treatments don't slow the underlying disease process. Researchers are now testing an array of new therapies intended to do just that.**

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Summer 2005 - Elisabeth Harvey, 85, is not your typical Alzheimer's patient. Sure, she reads the daily newspapers, forgetting that she just read them. But five years after she was diagnosed with Alzheimer's disease, she still lives at home, dresses herself and fixes her own lunch. What's more, her cognitive-test scores have not declined in over two-and-a-half years. "That's unheard of," says neuropsychologist Paul Solomon of the Memory Clinic in Bennington, Vt. How is it possible? In late 2002, Solomon enrolled Harvey in a trial for an experimental drug called Alzhemed, which she's taken ever since, along with the standard Alzheimer's drug Aricept. "Not everyone in the trial performed as well as she did," Solomon cautions. But still, he has to credit the test treatment. If not for the drug, he says, Harvey might well be in a nursing home by now.

Alzheimer's is a progressive, devastating and incurable illness. It afflicts some 4.5 million Americans at a cost of \$100 billion a year. That number is expected to hit 14 million by 2050. But delaying people's symptoms by five years could reduce the burden by half—and if better treatments could help patients like Harvey stay out of nursing homes, that would mean even greater savings in both cost and human anguish. These are becoming real possibilities. Bill Thies, vice president of the Alzheimer's Association in Chicago, foresees the day when everyone will have a routine brain scan for Alzheimer's at the age of 55 and begin a treatment program if there are signs of trouble, much as they do for heart disease today. When will it all happen? "I'll see it in my lifetime," the 63-year-old Thies replies, "provided I don't take the wrong cab in Chicago."

Part of his optimism stems from the nature of the treatments that are in development today. Whereas current drugs serve mainly to mask symptoms for a while, researchers are now mounting direct assaults on the underlying disease process. Most of the experimental treatments focus on taming a toxic protein called beta-amyloid, or A-beta. It's the main constituent of the sticky plaques that gum up Alzheimer's brains. Everyone has some of these plaques after a certain age, but Alzheimer's brains generally have many more. There are two basic ways to keep from reaching crisis levels. As Dr. Dennis Selkoe, a neurologist at Harvard's Brigham and Women's Hospital, puts it, "If you want to stop a bathtub from overflowing, you either turn off the spigot or open the drain. With Alzheimer's, you can reduce the formation of A-beta or help clear out what's already there." There are a score of potential new ways to do that. Even if some of them ultimately fail in testing, others seem likely to pass. Here are some of the more intriguing:

1. Most of the next-wave treatments are what Selkoe would call drain openers. Alzhemed, the experimental drug that Elisabeth Harvey received, acts as a magnet for strands of A-beta. Instead of clumping together and later forming plaques, they bind to the drug and filter harmlessly out of the body. In Harvey's trial, A-beta declined by an average of 20 to 35 percent in the spinal fluid of those who received treatment—and the decline in A-beta often translated into clinical benefits. Seventy percent of those with mild Alzheimer's held steady in cognitive testing for close to two years. Unfortunately, those with moderate disease continued to decline. "We presume there's too much damage by then to help," says Denis Garceau, senior vice president of Neurochem, the company that makes the drug. Larger trials are now underway. If all goes well, Alzhemed could be on the market in five years.

2. There are other ways to clear A-beta, at least in theory. In 2002, doctors Norman Relkin and Marc Weksler of Weill Cornell Medical Center discovered that the immune system makes antibodies against amyloid, but that Alzheimer's patients have lower levels. What if you could raise them? In a pilot study, Relkin gave eight patients six monthly injections with a natural blood product called intravenous immunoglobulin (IVIg), which contains the antibodies. His goal was simply to boost antibody levels, but he says the patients' family members found them more alert, engaged and articulate. "It was like turning back the clock a year," he says. Elan Corp. and Wyeth are now testing a bioengineered version of an amyloid antibody. They have started human trials, but approval is still at least four years away.

3. Opening the drain is a start, but if you could shut off the spigot at the same time, you might get even better results. Scientists have long known how to block gamma secretase, an enzyme that helps make A-beta. Unfortunately, the enzyme also makes dozens of proteins that are critical for brain function. How do you nix the bad without knocking out the good? Scientists at Torrey Pines Therapeutics screened 80,000 compounds to find one that would gently tweak gamma secretase to block A-beta production alone. In fact, they singled out a compound that blocks only the most toxic, long-chain versions of A-beta, not the less harmful shorter forms. The drug is not in human trials yet, but stay tuned.

4. In a novel approach that most scientists say comes out of left field, a new company called Voyager Pharmaceutical Corp. is using hormones to reduce amyloid formation. Dr. Richard Bowen, a family practitioner in Florida, stumbled on the approach when a patient noted that her husband's Alzheimer's hadn't worsened for five years, since he had begun taking a hormone treatment called leuprolide for his prostate cancer. The drug inhibits secretion of hormones called gonadotropins, which surge at menopause and skyrocket in people with Alzheimer's. Voyager has refined the drug for Alzheimer's, and early trials look promising, but larger studies are needed.

5. Others researchers are gambling on more radical approaches that wouldn't reduce A-beta, but build the brain's defenses against another hallmark of the disease: neurofibrillary tangles. These tangles cause the collapse of so-called microtubules, structures inside cells that help the cells maintain their shape. When microtubules collapse, brain cells can no longer transmit messages from one cell to the next. But Dr. John Trojanowski of the University of Pennsylvania's Alzheimer's Disease Center is studying drugs that may help reinforce the microtubules. He's most excited about the cancer drug Taxol, which could fight both cancer and Alzheimer's by the same mechanism. Cells with rigid microtubules are less prone to uncontrolled division, he says, and less likely to collapse. So far, Trojanowski has tested the idea only in mice. But Taxol is FDA approved. So if the animal work goes well, scientists should be able to skip human safety tests and go straight to large clinical trials with Alzheimer's patients.

6. If that sounds ambitious, Dr. Mark Tuszynski of the University of California, San Diego, has the most dramatic approach of all—gene therapy. In a much-heralded trial published this year, he injected eight patients' brains with specially engineered skin cells that work as tiny pumps, churning out nerve-growth factors that prevent the withering of brain cells. Almost two years later, patients showed greater neural activity on PET scans than untreated patients. "Most intriguing, disease progression slowed by 36 to 51 percent," says Tuszynski. "Even in the presence of amyloid, growth factors can prevent cell death or slow it down." But he notes that the treatment is still highly experimental—and because it is so invasive, it will have to prove more effective than other therapies to win approval or acceptance.

7. While these scientists hunt for better treatments, others are hoping to keep people from developing Alzheimer's in the first place. Dr. Gary Small, director of the Center on Aging at UCLA, has developed a way to scan brains for both plaques and tangles. His ultimate goal is to predict who's headed for trouble and start those patients on a preventive program, including a healthy diet, exercise and anti-inflammatory drugs, which in large population studies appear to correlate with risk reduction. Scientists are starting to figure out why. For example, neuroscientist Greg Cole at UCLA has found that the fish oil DHA lowers levels of A-beta, at least in mice. Intriguingly, it appears to both reduce production and enhance clearance of the toxic substance.

None of these treatments or preventive measures will banish Alzheimer's, any more than science has eliminated heart disease. But together, they could one day make it a manageable ailment—something it is not at present. When doctors told Marty Bahr, 56, of Bartlett, Ill., that he probably had Alzheimer's, his wife actually hoped that they would find a brain tumor or rare blood cancer instead—"something we could actually *do* something about," she says. If scientists succeed, wishes like that will one day be unnecessary.

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