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By SHARON BEGLEY

## **Fevered Debate Over Alzheimer's Origins Causes Deep Divisions**

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Although the exchange did not quite descend to the level of name-calling, it was not what you usually hear at scientific conferences. Halfway into a debate on whether Alzheimer's disease is caused by the accumulation in the brain of sticky "plaques" made of a protein called beta-amyloid, as the leading theory holds, and whether therapies that target amyloid are the best bets, one scientist let loose.

"I think your treatment will kill people," said neuropathologist Mark Smith of Case Western Reserve University, Cleveland, referring to anti-amyloid therapies. To which neuroscientist Todd Golde of the Mayo Clinic, Jacksonville, Fla., responded, "Ethically, I would say you're not in the right place."

Behind the scenes at last month's 9th International Conference on Alzheimer's Disease (the amyloid debate was not part of the official program), you could almost trip on the ideological lines drawn in the sand.

Beliefs about what causes this merciless disease have taken on such a religious fervor that one group is called tauists, after a protein called tau that forms "neurofibrillary tangles" inside the neurons and, say these scientists, kills neurons responsible for memory and thought. Another is called baptists, after the beta-amyloid protein that forms plaques around brain neurons and, say its accusers, causes neuron-killing tau tangles or kills neurons directly, or both. Apostates think amyloid plaques sop up neurotoxic proteins along with poisonous metals such as zinc and copper, and that eliminating plaques could therefore harm patients. Hence Dr. Smith's accusation.

As <http://online.wsj.com/article/0,,SB108206188684384119,00.html?mod=article-outset-box> I wrote last April, there are growing doubts that amyloid is guilty as charged. Autopsies of people with early-stage Alzheimer's show that the tangles form first, before plaques, in brain regions initially affected by the disease. "If you look at the evidence, it's the tangles that cause neuronal degeneration, and they come first, before the amyloid," says neurologist Patrick McGeer of the University of British Columbia, Vancouver, who was awarded one of the Alzheimer's Association's top scientific prizes at the meeting.

Another problem for the amyloid dogma is that "almost all aged brains have extensive amyloid deposition, even in people who die with no symptoms of Alzheimer's," says neurologist Peter Davies of the Albert Einstein College of Medicine in the Bronx. Worse, adds neurobiologist Nikolaos Robakis of Mount Sinai School of Medicine, New York City, autopsies of the brains of Alzheimer's victims show that "plaques don't correlate with neuronal death.

The amyloid is here and the dead neurons are somewhere else."

The amyloid debate has taken on added urgency, for many Alzheimer's therapies now in the pipeline are predicated on the guilt of amyloid. A vaccine being developed by Elan Corp., Dublin, for instance, targets amyloid plaques; unfortunately, it also shrank the brains of many volunteers it was tested on. Drugs being developed by Eli Lilly & Co., Indianapolis, and Neurochem, Laval, Quebec, target amyloid, too.

"The question is, if we are successful in controlling amyloid, will we be successful in helping patients?," says Zaven Khachaturian, who ran the Alzheimer's program at the National Institute on Aging. "The field doesn't have a clue."

But it might soon. Scientists who believe that amyloid causes Alzheimer's have one indisputable fact on their side: Mutations in three genes which cause the familial, inherited form of the disease all pump up amyloid levels in the brain. Surely this proves amyloid's guilt?

In the huge diversity of views presented at the meeting -- there were 4,500 scientists and 2,000 presentations -- you could hear the beginnings of an answer. "There were some faint suggestions that these 'amyloid' mutations do something besides affect amyloid," says Dr. McGeer.

For instance, an Alzheimer's gene once thought to do nothing but make lots of amyloid turns out to have a second job, said Dr. Robakis: It also stabilizes proteins that help keep neurons alive. When this gene (it's called PS1) is mutated, it speeds the death of neurons by triggering those toxic tau tangles and by making neurons more likely to commit suicide. A second Alzheimer's gene, called APP and also thought to simply be a source of amyloid, also seems to moonlight. When mutated, it pushes neurons to change in ways that lead to suicide, finds Rachael Neve of Harvard Medical School, Boston.

In other words, mutations in "amyloid" genes wreak havoc in ways that don't involve amyloid.

Interestingly, suicidal neurons seem to release amyloid. Perhaps that has fooled scientists into concluding that the amyloid around dead neurons is the killer, when it is actually an innocent by-stander.

No existing drug stops, let alone reverses, the inexorable cognitive and memory decline of Alzheimer's. The one thing baptists, tauists and apostates agree on is that drugs that prevent the disease will not cure it, and drugs effective against early Alzheimer's won't be the same as those that work against late Alzheimer's. We'll need a whole armamentarium.

Will any of the treatments target amyloid? "If amyloid were the answer," says Dr. McGeer, "the disease would have been solved by now."

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