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By SHARON BEGLEY



Is Alzheimer's Field Blocking Research Into Other Causes?

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Jie Shen describes the past two years of her scientific life as "torture," but she can't say she wasn't warned. In the mid-1990s, as a young researcher in the lab of a Nobel-winning neuroscientist, she grew curious about alternatives to the leading hypothesis of Alzheimer's disease, and in virtually any other field she would have been free, even encouraged, to follow her scientific curiosity wherever it led. But her mentor warned her off. Alzheimer's, he said, is not like other fields.

She found that out the hard way during an odyssey that has finally culminated in the publication of an eye-opening paper. In a nutshell, a team led by Dr. Shen, a molecular geneticist and neurobiologist at Harvard Medical School, Boston, shut down two mouse genes whose human forms have been linked to inherited forms of Alzheimer's.

According to the leading theory of the disease, these so-called presenilin genes are involved in the production of beta-amyloid, a protein that forms gumball-like "plaques" in the brain. Those plaques, in turn, are widely thought to kill brain cells, erase synapses and memory, and lead, ultimately and often blessedly, to death.

But adult mice missing the presenilin genes, and hence the supposedly toxic amyloid protein, still suffered memory problems and brain-cell death, just as in Alzheimer's. Dr. Shen and her colleagues concluded that amyloid is something the brain likely needs in order to think, remember and keep neurons alive, not something that gums it up, as the "amyloid hypothesis" holds.

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CHECKUP

See drugs in the pipeline for treating Alzheimer's disease

When the Harvard scientists submitted their findings to two leading journals beginning in 2002, they hit a brick wall. One peer-reviewer shot back with a long list of criticisms that took them months to address. Another demanded they figure out the molecular mechanism behind the effects in the mice, and then when they did that, demanded yet more detail -- the mechanism underlying the mechanism, as it were -- something pretty

much unheard of for a paper of this kind.

"Powerful people in this field think that amyloid causes Alzheimer's and won't consider research that questions the amyloid hypothesis," says one of the Harvard scientists. Competing theories blame other proteins (including those called APP and tau), toxic metals, cholesterol or inflammation for Alzheimer's.

The Harvard team thinks it would have been nice for the world to know its results two years ago, not yesterday when they were finally published in the journal *Neuron*. "One day," says one of the *Neuron* authors, "I'll write a book, 'The Dark Side of Science.' "

Amyloid enthusiasts deny that they have formed some kind of cabal. They believe that amyloid offers the best shot at defeating Alzheimer's and so view the pursuit of other avenues as a waste of resources. But something else seems to be at work.

"Whenever you have a field with limited funding, and a small number of people with big egos who have everything invested in one idea, you have the right chemistry for one theory to become so pervasive nothing else can flourish," says Zaven Khachaturian, who ran research at the National Institute of Aging from 1977 to 1995. He calls the dominance of the amyloid hypothesis and the strangling of alternatives "one of the most important issues in science today."

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The result of the amyloid orthodoxy is that for 20 years this one hypothesis has ruled Alzheimer's, dominating the research of scientists seeking understanding and pharmaceutical companies seeking treatments. "The amyloid people are very powerful, and have been dogmatic in opposing alternative [hypotheses]," says molecular biologist Rachael Neve of Harvard.

Despite hundreds of experiments casting doubt on the neurotoxicity of amyloid, maverick and innovative ideas get crushed. As my colleague Bernard Wysocki reported in December, after Ashley Bush of Harvard broke with the amyloid camp, journals rejected his papers and funding agencies turned down his grant proposals.

"It has been very difficult to get funding for anything that's not based on the amyloid cascade, or to publish alternatives to the amyloid hypothesis in top-tier journals," says Thomas Wisniewski, associate professor of neurology and pathology at New York University School of Medicine in New York City.

Such dogmatism is usually a bad idea in science, and when it comes to Alzheimer's, the effect has been

nothing short of tragic. By putting almost all its eggs in the amyloid basket, the Alzheimer's establishment has impeded progress on the disease. Because research chasing the demon amyloid gets the lion's share of financial support and dominates the high-profile journals, anti-amyloid treatments receive most of the R&D support, too. Few other approaches to cures are in the pipeline.

"I think we've lost some time," says Dr. Wisniewski. Neuropathologist George Perry of Case Western Reserve University, Cleveland, draws an analogy to the criminal-justice system. "Executing beta-amyloid," he says, "leaves the killer loose in the brain."

Next week, I'll explore the failings of the amyloid hypothesis, and discuss what has befallen scientists who challenge it.

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