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Maverick Scientist Is Winning Converts on Alzheimer's

Dr. Bush Was Widely Derided When He Said Zinc, Copper Played Role in Disease

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BOSTON -- Ashley Bush, a 44-year-old researcher at Harvard Medical School, was pilloried after he put forth a radical theory of Alzheimer's disease in 1994.

"Worthless," wrote one scientific critic. Others have described his style as brash, his content as flimsy, and his ideas unworthy of being published. At worst, Dr. Bush recalled, it felt like "hate mail."

Over the years, he submitted 30 scientific papers that were rejected by scientific journals. Eight times, his grant applications were spurned by the National Institutes of Health.

Dr. Bush's theory is that the real culprit in Alzheimer's is a copper and zinc buildup in the brain -- an idea few scientists have looked at. He believes the accumulated metals mix abnormally with a protein called beta amyloid in the brain, oxidizing -- literally rusting -- and destroying nerve cells. Published in the prestigious journal *Science*; his hypothesis swiftly drew criticism because it ran counter to the leading theory that Alzheimer's disease is caused mainly by the protein clumps themselves. And by highlighting metals as the culprit, it drew scowls from some who thought it resembled a largely discredited theory that aluminum caused the disease. (He never saw aluminum as a culprit.)

Now scientists are giving Dr. Bush more credence. He has a five-year grant from the NIH and this year won an American Academy of Neurology prize for Alzheimer's disease research.

One big reason: He is on the trail of a drug that absorbs his culprits - the excess copper and zinc and dissolves the protein clumps in the brains of experimental animals. Dr. Bush has found a potential Alzheimer's treatment in a 70-year-old dysentery drug with a history of toxic side effects. What's more, he and his colleagues this month published their first human clinical trial showing the drug's promise. "It's like Drano," he says. "It blows them away."

The small trial's results are "significant" and "innovative," says Roger Rosenberg, a neurologist at the University of Texas Southwestern Medical Center and editor of the *Archives of Neurology*, which published the research.

Dr. Bush's odyssey shows how rejects in the world of science can sometimes re-emerge as important figures. The history of science in the last 50 years could be written with papers rejected by prestigious journals, observed Paul Lauterbur of the University of Illinois after he won the 2003 Nobel Prize for medicine. His original paper on his prizewinning achievement, magnetic resonance imaging (MRI), was initially rejected in 1973 by *Nature*, which later ran it

It's far from clear whether Dr. Bush has unearthed a new key to Alzheimer's that yields a treatment, or just a dry hole. Nobody knows if his drug will work any better than the handful of therapies on the market or the dozens more in the pipeline.

Alzheimer's is a degenerative brain disease, affecting about four million Americans in the U.S. alone. Although not considered part of normal aging, Alzheimer's attacks mostly elderly people. About 1 % of those aged 65 show symptoms, a rate that surges to nearly 50% by age 85. Its main feature is memory loss, but in advanced stages, the disease erodes personality, judgment, powers of speech and the ability to perform the functions of daily living.

Abnormal Proteins

The brains of Alzheimer's victims, when examined at autopsy, appear speckled with two kinds of abnormal protein. One is beta amyloid clumps between brain cells, known as plaques. The other is neurofibrillary tangles, or protein strands that look like knotted skeins of yarn, inside cells. Nobody knows for sure whether these clumps and strands are causes or merely byproducts of the disease. But to many mainstream researchers, the amyloid proteins are the leading suspects.

This is where Dr. Bush breaks from the crowd. He believes that amyloid clumps aren't the ultimate villain, but more of an accomplice in the relentless destruction wrought by the disease. "The classic amyloid cascade hypothesis is wrong," he insists.

In Dr. Bush's view, amyloid protein plays a helpful role in the brain: absorbing metals like a sponge. But in Alzheimer's victims, he contends, the metals overwhelm the protein. He believes that copper mixes abnormally with amyloid, releasing hydrogen peroxide and other toxic chemicals that damage the nearby cells. Some of that protein breaks free, becomes "rogue" amyloid and mixes with zinc to form clumps that leak more hydrogen peroxide. Thus he indicts metals as the real culprits. This theory is still controversial.

Some critics see his metals theory as mere speculation. "Based on science, there is no substitution for what Ashley says," says Bruce Yankner, professor of neurology at Harvard. "Ashley's ideas are interesting. But that's what they are -- interesting."

One problem in verifying Dr. Bush's hypothesis is the difficulty of measuring copper or zinc in the human brain. Many scientists believe trace amounts of metals exist in the brain, but Dr. Bush contends that excessive amounts build up in some aged people. Among unanswered questions is where the metal buildup comes from. Dr. Bush doesn't claim to know.

Among Alzheimer's baffling aspects is the fact that it might have multiple causes. A small fraction of the population carries rare mutant forms of certain genes that increase the risk of Alzheimer's. At the same time, many researchers believe that such things as nutrition, exercise and mental stimulation may also play a role in keeping dementia at bay.

In recent years, a handful of drugs have hit the market to treat Alzheimer's, from Pfizer Inc., Johnson & Johnson and other companies, but these offer limited relief. The big challenge is to bring drugs to market that attack the underlying cause of the disease. Because the ultimate cause of Alzheimer's is unknown, different theories have fueled the pursuit of different kinds of drugs. Some aim to prevent the "snipping" of amyloid protein into fragments that form plaques. Dr. Bush considers this misguided, since he believes it is the metals interacting with the protein that do the damage.

The son of Jewish refugees from Poland and Palestine who fled their homes for Australia during World War II, Dr. Bush grew up in Melbourne. As a medical student at the University of Melbourne, he started training as a surgeon, and then switched to psychiatry.

He was drawn to Alzheimer's after working in the mid-1980s as a young physician at a mental institution, where he saw 700 patients with dementia who were given little in the way of diagnosis or treatment. He started studying the possible role of zinc while in Melbourne. He was inspired by a University of Texas teacher; Christopher Frederickson, who detailed the presence of zinc traces in the brain. Dr. Bush saw that the zinc and the amyloid were in the exact same spots, giving him a clue that they were somehow inter-related. He stayed on the trail when he moved to Harvard and the affiliated Massachusetts General Hospital in 1992.

Working in the lab of neurologist Rudolph Tanzi, he found that by adding zinc to dead brain tissue in test tubes, the amyloid suddenly formed clumps that looked like Alzheimer's plaques. This was a possible clue that the metals also played a role in triggering the plaques in the living brain as well. Dr. Bush submitted the paper to the prestigious journal *Science*. Dr. Tanzi warned he was shooting for the moon. But the paper was published in 1994.

"He started out extremely lucky," says Dr. Tanzi, his co-author on this and other papers. More luck followed. He obtained some initial research funding from NIH, and from Prana Biotechnology Ltd., a Melbourne-based biotech he co-founded in 1997.

But Dr. Bush's luck soon soured. His work was "bucking conventional wisdom," says Dr. Tanzi. He drew attacks from mainstream Alzheimer's researchers who were asked to review his submissions to peer-reviewed journals. One of the reviewers, who are traditionally shielded by anonymity, was especially savage.

"I do not think the manuscript is worthy of being published in *Nature* or elsewhere," the reviewer wrote, blasting the manuscript as "worthless." Another critic chastised him for muddying the already turbid waters of Alzheimer's research.

Rising Frustration

By 1999, his frustration rose as grant funds ran low. Like many researchers in academia who lack endowed chairs, Dr. Bush isn't paid by Harvard. He runs his lab and pays salaries out of grants and other such funds.

He had hoped a grant from the National Institute on Aging, part of the NIH, would solve his woes. But Dr. Tanzi judged some of his protégé's proposals as flimsy and ill-crafted. While he admires Dr. Bush's originality and experiments, Dr. Tanzi says he remains dubious about some of his theories. Dr. Bush, he jokes, is considered the "wacky uncle" around the lab.

Meanwhile at closed-door NIH meetings, grant reviewers weren't so jocular. They issued a pointed challenge to his work, Dr. Bush recalls. He says these outside experts asked: "If you are so sure this is the cause of Alzheimer's disease, where is your drug?"

"Why am I having such a difficult time?" Dr. Bush recalls asking NIH after his rejections.

But it turned out that Dr. Bush had an ally at NIH. He was Stephen Snyder, a Ph.D. in pathology at the National Institute on Aging. Dr. Snyder oversees grant applications dealing with the origins of Alzheimer's. He heard reviewers complain because Dr. Bush's applications were long on brain chemistry and short on biology. Dr. Snyder passed all this along to Dr. Bush, and vowed to help Dr. Bush improve his applications.

It also turned out that Dr. Bush was indeed pursuing a treatment. Working with mice given a gene for Alzheimer's, Dr. Bush tested oral doses of a 70-year-old drug called Clioquinol, versus placebos. When Dr. Snyder learned of this, he quickly asked to see the data. After nine weeks, the treated mice had a 49% reduction of beta amyloid deposits.

"Holy Finoki!" Dr. Bush e-mailed Dr. Tanzi.

In late 1999, Dr. Bush sent a photographic slide of the results to the aging institute. Dr. Snyder remembers thinking, "Wow. This doesn't come along every day." The placebo mice had huge plaques. The treated mice had brains as clear as the day they were born." He recalls deciding, "I'm going to the wall for this."

Dr. Bush crafted his ninth NIH grant proposal. The review committee gave it a score in the top third -- not great, but enough to get a \$750,000, five-year grant.

"The mice came along at the right time," Dr. Snyder says. The journal *Neuron* published the mouse study. In Melbourne, Prana, the biotech company Dr. Bush co-founded, prepared to launch human clinical trials.

But there was a problem: Clioquinol had a disastrous history. It was introduced in the 1930s by Swiss drug giant Ciba-Geigy AG, as a treatment for amoebic dysentery, a potentially deadly intestinal ailment. The drug was later promoted in Japan for all types of stomach trouble. By 1970, however, nearly 10,000 people who had been treated with the drug, mostly in Japan, developed paralysis or blindness.

These days, some scientists believe the adverse effects might have been influenced by a vitamin B-12 deficiency in the postwar Japanese diet. So Prana added vitamin B-12 supplements to the Clioquinol in the Alzheimer's study. That did the trick, the company says.

Prana's randomized double-blind clinical trial was launched in 2000 and completed by 32 volunteers in 2002. Half of them got Clioquinol; half got a placebo. In spring of 2002, Colin Masters, chairman of Prana's scientific board, gave the first peek at the results, declaring Alzheimer's disease was slowed by the drug.

This month the *Archives of Neurology* published the full report. The results: Volunteers on placebo showed a "substantial worsening" of the disease based upon cognitive tests, while people on Clioquinol experienced "minimal deterioration." In addition, blood levels of beta amyloid protein in the blood declined among those taking the drug but increased in those on placebo. As for side effects, the drug was "well-tolerated," wrote Dr. Bush and his co-authors from the U.S., Europe and Australia. One participant, who had a history of hypertension and glaucoma, suffered impaired vision during the trial. But the symptoms disappeared when the trial ended.

Now scientists in the U.K., Japan and the U.S. are pushing forward with research on Clioquinol or drugs like it. Doctors at Duke and Thomas Jefferson Universities are planning large-scale clinical trials. There are some glitches. Prana is in a patent dispute with onetime collaborators at a Greek pharmaceutical company, PN Gerolymatos SA. (It didn't respond to requests for comment.) Meantime, Prana is working on a drug similar to Clioquinol.

In retrospect, Dr. Bush concedes he was treated fairly by the NIH. "I just chose to pursue a subject that defied fashion," he says. "A good scientist needs a thick skin and an irrational sense of optimism."