involved in some cancers, such as melanoma," he says, "but it's not 'the biggie'" everyone is looking for on 9p21. Kamb, meanwhile, is sticking to his guns about *p16*. "I've never doubted that this gene was a major player in cancers of many kinds," he says.

Kamb has other recent evidence in his favor: studies suggesting that loss or inactivation of *p16* contributes to the development of at least two additional cancers. Takahiro Mori, Yusuke Nakamura, and their colleagues at the Tokyo Cancer Institute and Tohoku University School of Medicine in Sendai report in the 1 July issue of *Cancer Research* that the gene is mutated in 14 of 27 esophageal cancers, but not in the surrounding normal tissue. And in the September *Nature Genetics*, a team led by Scott Kern of Johns Hopkins University School of Medicine reports finding mutations or deletions of the gene in about 75% of the human pancreatic cancers they've examined. "It's a tumor suppressor, and it's important," Kern concludes. If results like those continue to flow in, the *p16* mood may yet swing back to euphoria.

–Jean Marx

NEUROSCIENCE

Alzheimer's: Could There Be a Zinc Link?

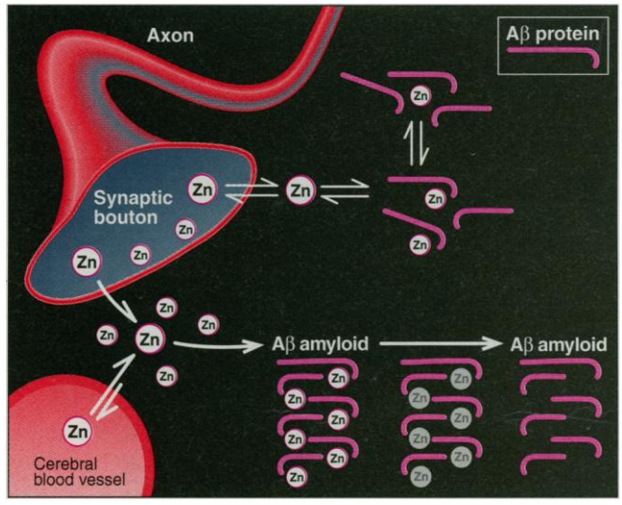
The effort to understand the causes of Alzheimer's disease has been so long and so frustrating that researchers have resorted to some unusual lines of inquiry. In 1991, for example, motivated by reports that zinc improves mental alertness in the elderly, a team in neuroscientist Colin Masters' lab at the University of Melbourne gave zinc supplements to a handful of Alzheimer's patients and age-matched controls. The results, however, were disastrous: Within 2 days, the cognition of the Alzheimer's patients deteriorated markedly.

To avoid further harm, Masters' team immediately halted the study, without having a chance to learn much about the biochemistry behind the disturbing results. Now, however, some researchers have taken a different approach—using a test tube—and have offered direct biochemical data hinting at a zinc-Alzheimer's connection. On page 1464 of this issue, Ashley Bush, a postdoc working with Rudolph Tanzi of Harvard University's Massachusetts General Hospital, and his co-workers report that zinc ions can cause one form of the Aβ protein (Aβ) to form clumps resembling the amyloid plaques found in the brains of Alzheimer's patients. Bush, a former graduate student in Masters' group, says, "We believe this information is going to be very important to people who are trying to develop strategies either to prevent or reverse amyloid formation."

Other researchers, though they hail the intriguing nature of this work, stress that it's very preliminary—and only from the test tube, which may not reflect real-life conditions. "It's a very interesting finding," says Alzheimer's researcher Steven Younkin of Case Western Reserve University in Cleveland, "but it's clear that it in no way proves zinc is the cornerstone of Alzheimer's. It's more in the realm of raising a very intriguing possibility." Younkin and others also cautioned that it's far too early for anyone to think about removing zinc from their diet.

Tanzi's group began the current work in 1992 after Bush joined the lab. Scientists had known Aβ was the main constituent of Alzheimer's plaques, and had recently shown that Aβ is present in a soluble form in cerebrospinal fluid. What, then, made the protein clump together in plaques only in the brain? Tanzi's team, mindful that zinc is important in the brain, decided to see how readily zinc and other transition metals could bind to Aβ and prompt formation of amyloid clumps. Zinc, they found, had by far the most significant effect.

At low concentrations such as those found in cerebrospinal fluid, zinc bound to Aβ without causing it to clump and precipitate out of solution. But when zinc was present at a concentration just above that, the peptide suddenly clumped. The clumps were similar in size to naturally occurring amyloid plaques, and they looked the same when stained and viewed with polarized light. Zinc did not have this effect on Aβ produced by rats, which do not develop amyloid plaques as they age—and whose Aβ differs from the human version by three amino acids. In the brain, Tanzi says, it's quite plausible that if the strict regulation of zinc broke down, sufficient concentrations of zinc could contact Aβ and form it into clumps.



Metal in the mind. If zinc is involved in the formation of amyloid plaques, high concentrations of the metal at the end of the axon—the synaptic bouton—could be the trigger, as shown in the pathway at left.

Critics, however, have a number of questions about the paper's conclusions and about the zinc-amyloid hypothesis in general. Carl Cotman of the University of California at Irvine notes that while the Tanzi study used free zinc ions in solution, in the brain zinc is bound to other proteins and may not be available to react with Aβ. And zinc may not be needed at all: At sufficiently high concentrations, Aβ can aggregate spontaneously, and Younkin's group recently reported that some Alzheimer's patients have elevated levels of a longer form of the protein that self-aggregates at a high rate in vitro (*Science*, 27 May, p. 1336).

In addition, Zaven Khachaturian, who heads the National Institute on Aging's Alzheimer's program, cautions that the long-debated question of whether Aβ amyloid is really a key element in causing Alzheimer's or whether the plaques are a secondary consequence of other disease processes is still very much up in the air (*Science*, 4 September 1992, p. 1336). "There are many major, gaping holes in the amyloid hypothesis," he warns.

Still, the new zinc data are important, says Alzheimer's researcher Dennis Selkoe of Harvard University. He and others would now like to see similar experiments done with solutions that more closely mimic the environment of the brain—tests the Tanzi group is already pursuing.

But while tests continue, researchers—including Tanzi—worry about the public's reaction if the results are overplayed in the media. A decade ago, they recall, research proposing a link between Alzheimer's and aluminum—a link now regarded as highly questionable—caused many people to throw aluminum and Silverstone-coated pans in the garbage. Tossing out cookware might be expensive, but it's not dangerous. But removing zinc, a metal that is important to health, from one's diet could have serious repercussions.

–Jocelyn Kaiser