Hints of a Brain Toxin in Alzheimer's

Scientists have found the first evidence that protein deposits in the brains of people with Alzheimer's disease may contain a compound toxic to nerve cells. It remains unclear whether their experiments, performed on cultured cells, reflect the situation in living brain tissue. Nonetheless, the findings offer tantalizing new clues about Alzheimer's potential underpinnings, supporting the hypothesis that a glitch in the biochemical processing of a normal brain protein causes the debilitating, neurological disease.

Despite a decade of research, the cause of Alzheimer's continues to elude scientists. In particular, researchers are vexed by their inability to determine whether the protein-rich deposits, or plaques, seen in Alzheimer-afflicted brains are a cause or a by-product of the disease. Plaque formation is accompanied by brain cell death, progressive memory loss and dementia.

Rachael L. Neve of the Harvard Medical School in Boston knew that amyloid – a protein present in relatively small quantities in normal brains – is the major component of Alzheimer's plaques, and that each piece of amyloid is a fragment of a much larger protein common in normal brain tissue. She and her colleagues genetically engineered cells to mass-produce amyloid, and found it had no effect on healthy neurons in culture. But with a little more genetic tinkering, the researchers reprogrammed their cells to secrete a slightly longer protein fragment – one made of the amyloid segment and 63 additional amino acids that normally adjoin it within the large, precursor protein. The new protein proved deadly to cultured nerve cells.

"We want to be very cautious about saying that this piece is involved in Alzheimer's disease," says Neve. Scientists so far have found only indirect evidence of her augmented amyloid in the brains of Alzheimer's patients. However, other experiments indicate that normal brain enzymes could easily cut her fragment from the amyloid precursor protein. Neve says the toxic fragment's structure suggests that in most people it would remain safely embedded in a nerve cell membrane, rendering it harmless. But in Alzheimer's patients, a cellular defect might allow its release. "It's possible that this [neurotoxic piece] could be generated first and then get further broken down to produce what's in the plaques," she says.

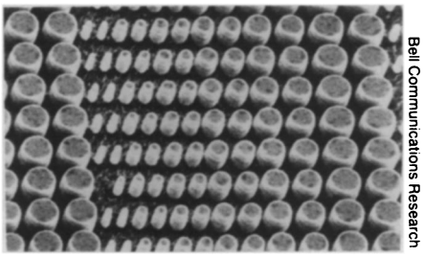
Other researchers agree that Neve's work, described in the July 28 SCIENCE, is the first to associate any neurotoxic effects with an amyloid-related protein. But it has yet to be reconciled with findings published in the March 17 SCIENCE by University of California, Irvine, researcher Carl W. Cotman and colleagues. They chemically synthesized a closely related amyloid fragment that temporarily *enhanced* nerve growth.

"The story is going to be fairly complicated, and there may be a variety of different functions served by these different fragments of the larger molecule," Cotman says. Nonetheless, he adds, Neve's use of living cells to produce her fragment is "a lovely methodological approach" that will prove useful as scientists seek to create and test other potentially significant Alzheimer's proteins.

If ongoing experiments confirm a role for Neve's protein in Alzheimer's, further research could lead to the development of drugs capable of blocking its effects, she says. – *R. Weiss*

Growing and carving micro-laser forests

On a dime-sized chip, researchers have created a high-tech forest of 2 million cylindrical lasers, each about a twentieth the girth of a human hair and a tenth of a hair-width in height. Likely the world's smallest lasers, the devices represent a stretching step toward harnessing light for speeding up computing and communications and for designing otherwise impossible light-based technologies, the scientists say.



Bell Communications Research

Tiny section of a semiconductor chip hosting 2 million lasers. Their diameters range from 1 to 5 microns.

As electronic chips get denser and faster, the wires that carry bits of data to and from them seem increasingly sluggish, especially for the ever-more-complicated problems and decisions now being relegated to computers. To ease the bottleneck, scientists have been looking toward materials such as gallium arsenide, which can transform electrical currents into beams of light zooming through optical fibers.

"The rate at which you can transfer information along an optical fiber is much higher than the [transfer] rate along an electrical wire," notes James P. Harbison, one of three researchers from Bell Communications Research in Red Bank, N.J., who are working on the project with four colleagues from AT&T Bell Laboratories in Murray Hill, N.J. Jack L. Jewell of AT&T initiated the project and unveiled the results July 18 at a conference in Kobe, Japan.

To create the laser forest, the scientists start with a technique called molecular beam epitaxy to grow semiconductor chips with a composition they can regulate at each molecular layer. Using a relatively thick layer of gallium arsenide as a crystal template, they stack alternating layers of gallium arsenide and aluminum arsenide molecules to form two mirror-like regions. These mirrors will sandwich the lasers' light-emitting "gain medium," made of indium gallium arsenide.

The next job is to chisel individual lasers from the multilayered chip. After a thin coat of gold, which will serve as an electrical contact for pumping the lasers, the chip gets an icing of a photoresist material that toughens when illuminated. Shining light onto the coated chip through a polka-dotted mask, then washing away the unexposed photoresist icing, yields a polka dot photoresist pattern. A beam of xenon ions then cuts through the chip's photoresist-free parts like a cookie cutter, producing the 2 million multilayered microcylinders.

A gentle current (a thousandth of an amp) injected into the gold layer with an electrical probe pumps the lasers into action. Excited electrons travel through the top mirror into the gain medium, where they emit light as they combine with nearby sites of positive charge originating in the bottom mirror. The flanking mirrors return some of the light to the gain medium to stimulate emission of more light of exactly the same wavelength and phase.

Most existing semiconductor lasers are at least 50 times larger, emit light from their edges rather than their surfaces and require either higher electrical currents or other lasers to run them, Harbison notes. The smaller, more readily pumped, surface-emitting lasers should integrate more smoothly with electronic circuitry into hybrid "opto-electronic chips," he says.

"It's certainly a major step toward realizing these devices," comments laser-making physicist Paul L. Gourley of Sandia National Laboratories in Albuquerque, N.M. – *I. Amato*