NEUROBIOLOGY

New Lead to an Alzheimer's Mouse?

If an Alzheimer's researcher were to make a wish list, chances are good that a small animal model for the disease would be near the top. Alzheimer's develops naturally only in humans and higher primates, and the desire for an animal model—which would allow scientists to test theories about the cause of the disease as well as potential treatments—has spurred several efforts over the past few years to genetically engineer mice that would mimic Alzheimer's symptoms. Unfortunately, those efforts have not met with much success.

Now two groups of researchers may have taken a step toward fulfilling the wish for an "Alzheimer's mouse," by transferring into mice a human gene that's a prime suspect in Alzheimer's pathology. But it's only a first step: Although the gene is highly active in the animals, it has not yet produced pathological changes. The preliminary state of the research, combined with the troubled history of previous work— which includes retractions of two models, one amid concerns that tissue purporting to show Alzheimer's pathology in mice may have been of human origin (*Science*, 6 March 1992, p. 1200)—makes everyone cautious. "I really don't want to oversell it," says Alzheimer's expert Sam Sisodia of Johns Hopkins University School of Medicine, a member of one of the groups working on the current models. "It would be great if it works, but there's [no pathology] yet."

To try to create the mouse models, the two teams, one led by Johns Hopkins developmental geneticist John Gearhart and the other by Ted Choi of GenPharm International in Mountain View, California, used the human gene for the amyloid precursor protein (APP). APP may play a role in formation of the plaques that are one of the characteristic pathological features of Alzheimer's brains. Plaques consist of a protein core, composed mainly of the peptide β-amyloid, surrounded by degenerating nerve terminals. One school of thought holds that the deposition of β-amyloid, which is split from APP, causes the nerve degeneration of Alzheimer's, although the β-amyloid deposition might instead be merely the result of that degeneration.

Because of its proposed role in Alzheimer's, previous attempts at mouse model-making also used the APP gene, but the new work differs from those efforts in a significant way. The earlier research did not use the full APP gene because its 400-kilobase-length greatly exceeds the capacity of the vehicles then available for cloning DNA. Instead, researchers used DNA copies of APP messenger RNAs lacking the gene's usual control sequences as well as the noncoding introns needed for normal patterns of gene expression. Presumably as a result, the animals produced little human APP protein.

But earlier this year, several groups, including Choi's at GenPharm, developed methods of introducing into mice genes cloned in yeast artificial chromosomes (YACs). YACs have the capacity to handle full-length genes, and the Gearhart and Choi groups were able to use the new methods to put the complete APP gene into their mice. This makes it the largest gene genetically engineered into those animals to date. (The Gearhart team describes its work in the September *Nature Genetics* and Choi and GenPharm colleague Barbara Pearson have a paper in press at the *Proceedings of the National Academy of Sciences*.)

Both Gearhart and Choi say the initial results are encouraging. In particular, the animals make almost as much human APP protein as they do mouse protein. "We can show nicely that we have the human protein in neurons of the major cell groups in the animals' brains," says Gearhart. Nonetheless, neither group has yet seen any sign that their mice are developing plaques or other types of Alzheimer's pathology. It is possible that excess APP production may not be at fault in the first place, although Gearhart notes that people with Down's syndrome, who have an extra copy of the gene, develop Alzheimer's pathology early, around age 35. Or, the mice may simply be too young to show plaque formation: The oldest are 7 months old (mice usually live 2 to 3 years). But without the pathology, both groups acknowledge, they can't claim to have an Alzheimer's model.

Buoyed by the early findings, however, both teams are moving ahead to the next step, which is to insert into mice the mutant APP genes that have been linked to hereditary early-onset Alzheimer's in some families. Says Sisodia: "the strongest feature of the approach is that it allows us to test whether these mutations can cause pathology." If the efforts to produce an Alzheimer's mouse succeed, it would be "fantastic," says Zaven Khachaturian, who heads up the Alzheimer's research program at the National Institute on Aging. So, along with everyone else, he's watching closely. And hoping that the latest efforts don't follow the trend in this field—early promise followed by a quick flameout.

–Jean Marx

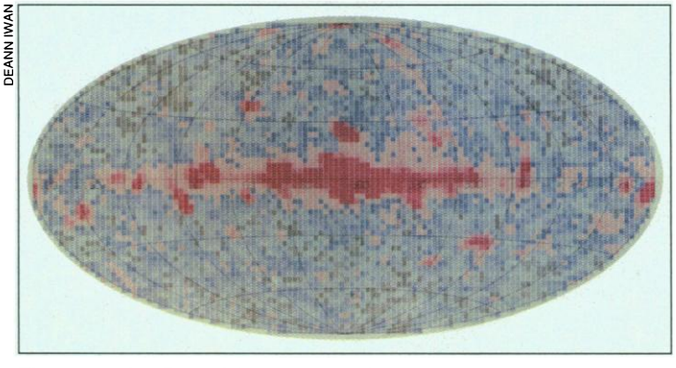
ASTRONOMY

Closing In on X-Ray Background Origins

When astronomers first ventured above the atmosphere with rockets and satellites 30 years ago, their instruments caught a cacophony of x-rays and gamma-rays. X-rays appeared to drizzle in from all directions in the universe, forming a ubiquitous but mysterious "x-ray background."

Now one group of astronomers think they have finally discerned the background's source: galactic powerhouses known as active galactic nuclei (AGN). These are powerful radiation-emitting sources such as quasars. In last week's *Astrophysical Journal*, Julian Krolik of Johns Hopkins University and his colleagues report that they analyzed new x-ray data from detectors on the Japanese Ginga satellite and NASA's Compton Gamma Ray Observatory that sampled a variety of these AGNs. The researchers made some assumptions about the general distribution of AGNs in the universe and concluded that the combined emissions of these sources would closely match the spectrum of the x-ray background. "Once we saw that the data did match, everything fell into place fairly quickly," Krolik said in a press statement.

Though some astronomers agree, critics point out that Krolik's calculations of AGN distribution rest on assumptions about the curvature of space and density of matter. Different assumptions have led another team to conclude that an additional class of sources may also contribute to the background.



DEANN IWAN

The x-ray sky. Powerful x-rays come from sources in our galaxy *(pink)*, and from beyond comes a background x-ray glow *(blue)*.

But whether or not Krolik and colleagues manage to satisfy their critics on the fine points, they are closing in on a longstanding question. The astronomer who first detected the x-ray background, Riccardo Giacconi,

suggested in 1979 that AGNs were the source. But a crucial test of his theory failed when the spectrum of background x-rays didn't match a spectrum that combined some of the closer quasars and other types of active galactic nuclei. That made it hard to argue that the background and the nuclei were related. Other theories, such as a hot, x-ray emitting gas in intergalactic space, were proposed and later discarded when contradictory evidence emerged.

Researchers, Krolik among them, then returned to Giacconi's idea, realizing the mismatched spectra could have been the result of instrument limitations. Previous measurements of the x-ray background showed that it consists of a wide range of x-ray energies. But the AGN spectrum in the test came from a satellite called HEAO1 that—Krolik suspects—only detected a narrower portion of that range from individual nuclei. The result: The AGN spectrum didn't match the background.

To get a more accurate spectrum, Krolik used better detectors on the Gamma-Ray Observatory and Ginga. He combined spectra from a handful of individual AGN and constructed a model of the x-ray spectrum that would result from millions of these scattered through space. To do that he assumed he had collected a representative sample and then extrapolated to the population at large, using satellite data on AGN population distribution. The data actually show the number of AGN at different red shifts, and to convert that data into a spatial distribution he had to make some assumptions about the distance scale and geometry of space. The model spectrum he got as a result matched up nicely with the spectrum of the background—and met the expectations and approval of some colleagues. "I expect there to be consensus within a year," says Columbia University astronomer David Helfand, who has reached similar conclusions from independent studies of the background.

But while this general idea seems acceptable, NASA-Goddard astronomers Elihu Boldt and Darryl Leiter differ on some details. They argue that Krolik's result ties up too much of the universe's mass in AGNs. Boldt and Leiter, making different assumptions about the geometry of the universe, conclude that in addition to AGNs, another class of sources also contributes to the background. They propose "precursor" AGNs, which shine at us from far out in space and far back in time.

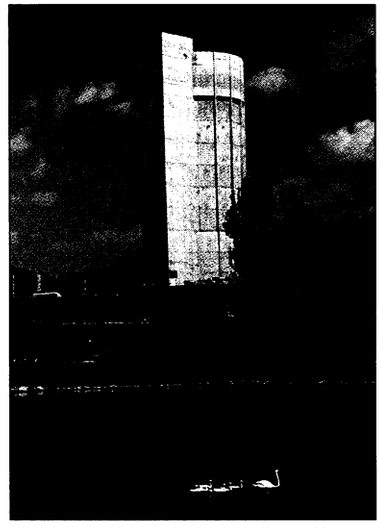
Boldt adds that his idea is just speculation, but it shows that the case isn't solved yet. At one time people proposed that the background came from everything from hot gases to exploding stars. Now it's narrowed down, says Boldt, but there's still room for debate at a more refined level. "The whole thing is in its infancy," he says.

–Faye Flam

MATERIALS SCIENCE

Holding the Lines in High-Temperature Superconductors

George Crabtree, who works on high-temperature superconductors at Argonne National Laboratory, recalls how a former student put his finger on the challenge that is now consuming Crabtree and his colleagues. When it came time for the student to defend his Ph.D. thesis, one of the first to be written on this new class of ceramics that can carry current without resistance at temperatures tens of degrees higher than earlier superconductors, he insisted on discussing magnetic lines of force as though the lines were real. That didn't go over well with the professors on his thesis committee. Unfamiliar with the nuances of superconductivity, they kept trying to explain to this misguided soul that flux lines are only emblems of magnetic field strength and direction. Like the lines on a contour map, they don't really exist.



OAK RIDGE

Big gun. Drilling angstrom-sized holes in superconductors has required massive accelerators, like the Holifield Heavy Ion Facility at Oak Ridge.

The problem is that in high-temperature superconductors, the flux lines *are* real. As magnetic fields penetrate a superconductor, they actually break up into lines: individual vortices, like the swirling whirlpools formed as the water drains out of a bathtub. Each vortex contains one quantum of magnetic flux—the minimum flux nature allows. And when electric currents flow through the material, these vortices can be torn from their moorings. As they move, they waste energy, create resistance, and cause the temperature at which the material loses its superconductivity to "drop like a rock," as physicist David Nelson of Harvard University puts it. Because many of the applications envisioned for these materials—in generators, motors, magnetic resonance imagers, and research magnets, for instance—would expose them to high magnetic fields, that's a major obstacle to realizing their much-heralded potential.

In principle, at least, researchers already have a solution to this problem: bombarding superconducting materials with ions to create holes tens of angstroms across called columnar or track defects. By capturing the vortices and pinning them in place, these defects enable the materials to retain their superconductivity in high magnetic fields at temperatures high enough—above 77° Kelvin—for liquid nitrogen, rather than liquid helium, to suffice as a coolant.

But this solution is far from perfect. Drilling the holes has required accelerators that can hurl heavy ions at energies of half a billion electron volts or more, machines far too rare and expensive to become part of any superconductor production line. By learning more about the physics of columnar defects and borrowing techniques from areas as far-flung as metallurgy and nuclear physics, however, researchers are developing ways to create the defects more cheaply and efficiently. Says Argonne materials scientist Mark Kirk, "It's one of the tricks everyone is trying to do."

The effort to pin down the flux vortices began when their show-stopping effect was first observed, soon after the 1986 discovery of high-temperature superconductors (*Science*, 26 May 1989, p. 914). The initial question, says James Thompson of Oak Ridge National Laboratory, was simply, How do you immobilize a line of magnetic flux? Because the core of a magnetic vortex isn't superconducting, a vortex is most "comfortable," energetically speaking, when it sits in a non-superconducting region of the material. The obvious approach to pinning the vortices, says Thompson, was to create such defects deliberately—to somehow destroy the superconductivity on a scale of a few tens of angstroms. In 1990, Thompson and colleagues from Oak Ridge and IBM bombarded superconducting crystals with protons, creating what Thompson calls a "rather dense array of random point-like defects"—sites where, say, an atom was dislodged from the crystal lattice.

The result was an order of magnitude increase in the amount of current the materials could carry in weak magnetic fields. At liquid nitrogen temperatures, however, the materials remained far too sensitive to increasing