Nuclear buildup may explain brain diseases

Almost 20 years ago, a team of scientists removed brain cells from people with the neurodegenerative disorder Huntington's disease and scrutinized them under a powerful electron microscope. Deep inside the cells, in the DNA-carrying sac called the nucleus, the investigators found mysterious clumps.

The report was "buried in the literature. Nobody paid any attention to it at all," says Gillian P. Bates of Guy's Hospital in London.

Somebody should have. Resurrecting that long-forgotten observation, Bates and her colleagues have studied mice genetically engineered to develop Huntington's disease and now report that the mutant proteins they produce aggregate in the nuclei of some brain cells. These protein clumps may harm the nucleus and lead to the cell's eventual death.

"We and at least one other laboratory do see these same lesions in Huntington's disease patients," adds Christopher A. Ross of Johns Hopkins Medical Institutions in Baltimore, citing preliminary observations in brain tissue removed during autopsies.

Other researchers have detected similar deposits in the brain cells of people with spinocerebellar ataxia type 3 (SCA3), another neurodegenerative disease.

These findings suggest that a common mechanism exists for the cell death seen in a whole family of brain diseases.

"We're now tying all these diseases together in that there's an alteration in the nucleus taking place because of mutant proteins. There's a unifying theme, at least to one step in the diseases," says Huda Y. Zoghbi of Baylor College of Medicine in Houston. She and Harry T. Orn of the University of Minnesota in Minneapolis have seen nuclear protein deposits in mice with a condition similar to the human disease spinocerebellar ataxia type 1.

The new research has offered hope to investigators seeking to thwart the inexorable decline of people with Huntington's disease and similar brain disorders. They speculate that physicians could cure or delay the diseases with compounds that reduce the buildup of the mutant proteins. "You might not need to slow it down much to have a dramatic effect," says David E. Housman of the Massachusetts Institute of Technology.

Huntington's disease and the other illnesses under investigation result from unusual mutations that some scientists call a genetic stutter (SN: 6/10/95, p. 360). In each disorder, a gene contains abnormally long stretches of DNA known as CAG repeats. The extra CAG repeats add copies of an amino acid, glutamine, to the protein normally encoded by the gene.

Last year, Bates and her coworkers created mice with an illness similar to Huntington's by giving them part of the mutant gene that causes the disorder (SN: 11/30/96, p. 348). In the Aug. 8 CELL, they report that weeks before symptoms strike the mice, spherical deposits appear in the nuclei of some of the animals' brain cells.

Tests showed that the clumps contained mutant versions of huntingtin, the protein encoded by the Huntington's disease gene. Moreover, the cells affected are the specific ones harmed by the disease, says Bates.

In the August NEURON, Randall Pittman of the University of Pennsylvania School of Medicine in Philadelphia and his colleagues report on postmortem studies of the brains of four people who had SCA3. In each case, antibodies showed that the mutant form of the protein ataxin-3 had formed large masses inside the nuclei of some brain cells.

Some scientists caution that the deposits may merely be a marker for other problems caused by the mutant proteins.

"It's really hard to believe that a cell can function properly when its nucleus has that big an aggregate sitting in it. The nucleus just doesn't have that much space to spare," says Pittman. "Still, we have to make sure that the nuclear aggregates are the real culprit. I don't think anyone has proved it."

Pittman and other researchers have started to develop laboratory systems in which they can study the formation of the protein deposits and test compounds that may stop the accumulations.

In the Aug. 8 CELL, for example, Eberhard Scherzinger of the Max Planck Institute for Molecular Genetics in Berlin and his coworkers describe test-tube studies in which mutant forms of huntingtin aggregate into a fibrous deposit.

The proteins' tendency to clump "looks like an inherent consequence of the long glutamine stretches," says Housman, noting that the glutamines may join the proteins in a zipperlike fashion.

Pittman contends that the mutant proteins may also bring other molecules into the fold. "Once these aggregates start forming, they can recruit normal proteins," he says.

Scientists are puzzled as to why mutant huntingtin proteins pile up inside nuclei, since the normal form of the protein seems to reside outside them. "We want to know how the proteins get in the nucleus," says Bates.

Also still unanswered, she adds, is why only some brain cells develop the nuclear deposits. —*J. Travis*

High vacuum produces ultrapure crystals

For electrons zipping through a semiconductor, cleanliness is next to speediness: The fewer impurities in the material, the faster the electrons move.

A team of researchers has applied this rule of thumb to gallium arsenide, the semiconductor material used in the laser elements in compact disk players. By growing gallium arsenide crystals nearly 25 percent purer than those previously made, the group recorded a maximum electron speed of 14.4 million centimeters per second.

Although silicon is by far the most widely used semiconductor today, gallium arsenide has advantages in certain applications. It can emit light, hence its utility in lasers. It can also be used at high frequencies, making it ideal for radio-frequency electronic components in cellular telephones.

The improvement in purity "is more of a technological feat than a scientific breakthrough," says Mordehai Heiblum of the Weizmann Institute of Science in Rehovot, Israel. He and his colleagues improved the vacuum system used to grow their samples, thus significantly reducing the number of contaminants. The samples consisted of multiple alternating layers of gallium arsenide and aluminum gallium arsenide. A group at Bell Laboratories set the previous purity record in 1989.

Impurities act as roadblocks that scatter the moving electrons, thus reducing their speed. In order to see the effects of unwanted atoms most clearly, the researchers recorded the electron speeds at a very low temperature—just one-tenth of a degree above absolute zero.

At higher temperatures, the thermal vibrations of atoms have a greater effect than impurities. "If you want to avoid scattering of electrons from these thermal vibrations, you cool [the sample] down as much as you can," says Heiblum. The group reports its findings in the Aug. 4 APPLIED PHYSICS LETTERS.

Real devices used today operate at room temperature, so impurities don't significantly limit electron flow. As electronic devices get smaller, however, the number of impurities becomes critical, he adds.

Ultrapure crystals are important for studying how electrons travel in a material. In their gallium arsenide crystals, Heiblum says, the electrons travel a very long distance—120 micrometers—before scattering. Over these path lengths, the electrons display wavelike properties. When they travel short distances before scattering, the electrons act more like particles.

"We scientists like to study the behavior of electrons at their quantum mechanical limit, because then they interfere and diffract and do all kinds of things that we never see at room temperature," Heiblum says. —*C. Wu*