Michael Reese News

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Secret to Alzheimer's disease lies deep inside cells

By Theodore Berland

A Michael Reese doctor is looking deep within the structure of brain cells to find the secret of the tragically baffling disease called Alzheimer's.

Dr. Audrius V. Plioplys believes that unlocking such secrets will lead to prescient diagnosis and effective treatment of the disease.

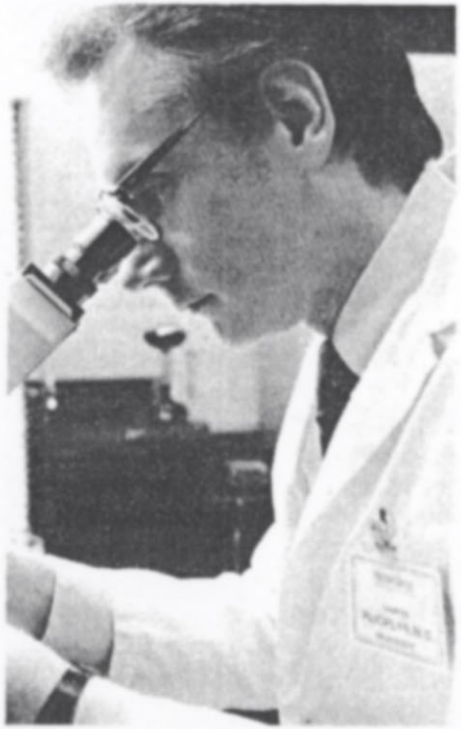
The 38-year-old neurologist joined the medical center in January to direct the only laboratory in this area conducting basic research in Alzheimer's. He will also treat other nervous disorders in both children and adults.

His years of research conducted at Laval University (Quebec), and the University of Toronto have given him a solid base upon which to build his new program at Michael Reese. He explains that after he completes the hiring of his staff, the setting up of his laboratory, and a few grant proposals, he will essentially follow two lines of investigation involving cells. One is the microscopic study of the brain cells of mice which have a version of Down's syndrome. The second is the study of the skin and blood cells of Alzheimer's patients. Dr. Plioplys emphasizes that his research is aimed at the goals of developing new tests to diagnose the disease and to screen potential treatments.

He explains, "The brains of all Down's syndrome persons who live to about 40 years of age suffer changes associated with Alzheimer's disease. They lose their abilities to function, their memory, and their skills, just as non-Down's syndrome-Alzheimer's patients do. Since Down's is a genetic condition associated with an extra chromosome, it made me wonder whether Alzheimer's is also genetically-linked. In Toronto four years ago, I examined the cells of autopsied brains of infants, four months of age and younger, both normal and with Down's syndrome, who had just died of other causes. The microscope showed significant abnormalities in Down's syndrome brains."

These microscopic abnormalities were in the structure that gives each living cell the shape characteristic of its type. Called cytoskeletons, cells would be formless blobs without them. Cytoskeletons are analogous to bony skeletons except that they are microscopic and made not of bone but of networks of long filaments of protein. Besides giving the cell shape, these filaments also distribute nutrients inside the cell.

"In Alzheimer's disease," Dr. Plioplys explains, "certain substances which accumulate in abnormal quantities are related to the cytoskeleton. These paired helical filaments, as we call them, can be seen with the help of an electron microscope. There are many more of these filaments in the cells of an Alzheimer's patient's brain than there are in the cells of a normal brain. This suggests some sort of abnormality in regulation. Detecting cytoskeletal abnormalities in Down's syndrome infants' brains made me think that this perhaps is a lifelong process. It seems possible that in Down's syndrome patients, a process of misregulation sets the stage for the cytoskeleton to simply break down and clog up the cell's machinery. Perhaps the same error of regulation occurs in normally developed persons who have Alzheimer's."



Dr. Audrius Plioplys searches for fibroblasts in a tissue culture of an Alzheimer patient's skin.

To learn more about abnormalities in Alzheimer's brain cells, Dr. Plioplys has grown animal brain cells as a single tissue layer on the inside walls of rectangular-shaped glass bottles. The choice of cells he could use in such tissue cultures was limited since brain cells essentially stop multiplying after birth. So he grew cultures of tissue of the brains of fetuses of a special strain of mouse bred to have a Down's-like syndrome. Whereas in the human, Down's is associated with a third, or extra, 21st chromosome, this mouse has an extra 16th chromosome.

"What gene on the extra chromosome does this?" Dr. Plioplys asks, abstractly. "I think this has something to do with what are called alpha and beta interferon receptors. Interferon is a family of natural substances that the body produces to fight viral infections. I am interested in it because this

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substance can slow a cell's growth and migration in the embryo and has effects on the cytoskeleton.

"Because Down's syndrome persons have 50 percent more chromosomal material, they have 50 percent more interferon receptors. But they have more than 50 percent interferon sensitivity in their cells. In fact, when we place interferon on tissue culture cells of Down's syndrome mice we find an 8-to-30 times sensitive amplification. That's a tremendous increase in response. So maybe the same genetic flaw that causes Down's syndrome cells' special sensitivity to interferon also causes the cytoskeletal abnormalities which lead to Alzheimer's.

"Before coming here, I followed this lead by placing a substance which blocks interferon into cultures of fetal Down's mouse cells to see if it would correct abnormalities of the cytoskeleton, and it did. This is important for two reasons. First, it showed how tissue cultures can be used as a model for studying cellular abnormalities associated with Alzheimer's. Second, it showed how this tissue culture model can be used to screen potential medications for Alzheimer's."

His success with the tissue cultures of fetal mouse cells led Dr. Plioplys to his next step. He is growing cultures of tissues from the skin of Alzheimer's patients. He explains, "Alzheimer's is not just a brain disease. We see certain abnormalities also in the fibroblasts of Alzheimer's patients' skin cells. That means we might be able to view skin cells under the electron microscope and develop this as a means of early detection and diagnosis of Alzheimer's. So this could lead to what we would term a reliable peripheral marker for the disease. Furthermore, these skin cultures may also provide a laboratory, or in vitro, means of testing the effects of new drugs on Alzheimer's cells."

Another area of investigation is the immune system in Alzheimer's disease. He explains, "Brain samples taken from Alzheimer's disease patients have shown evidence of immune activation. It is possible that the immune system plays a role in the death of brain cells in Alzheimer's disease." To test this possibility, Dr. Plioplys is taking samples of Alzheimer's patients' blood to see if blood cells—which have the same immune components as other cells of the body—have any immune activation. He feels that if this is so, tissue cultures of blood cells could be used to screen the many drugs which act on the immune system for possible use as Alzheimer's disease treatment.

Dr. Plioplys explains that he is motivated by the patients he cares for. "It's sad to see these once vital people developing the disease. The amount of deterioration in a year is often shocking. They develop memory problems, lose their manual skills, and can't do the most elementary acts of caring for themselves. There are at least two million such people in the United States today. You know, we would be thrilled if we could reverse the Alzheimer's process and save a patient. We would be happy to be able to slow down the Alzheimer's process and spare the patient a few more years. We would be ecstatic if we could detect a person's propensity to developing Alzheimer's and then prevent it completely. That is a long way to go, but we are working toward that goal."

Dr. Audrius Plioplys, neurologist, joined Michael Reese Hospital and Medical Center in January to direct the only laboratory in this area conducting basic research in Alzheimer's disease.