How Down's damages the fetus

SCIENCE/MEDICINE

Links with Alzheimer's discovered; syndrome prevention and therapies are on distant horizon, doctors say

BY MARVIN ROSS
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MEDICAL researchers believe they are beginning to understand how the physical manifestations of Down's syndrome occur and perhaps also those of Alzheimer's disease. They have found links between the syndrome and Alzheimer's and have also developed an animal model for Down's.

On the distant horizon, the researchers hope to prevent the two conditions and also develop therapies for those who already have them.

"Basic neurobiologic explanations are opening up avenues of potential therapeutic interventions of Down's syndrome," says Audrius Plioplys, a neurologist at Surrey Place Centre and the Hospital for Sick Children in Toronto.

The work of Dr. Plioplys and his colleagues also has considerable implications for possible drug intervention in Alzheimer's disease and in aging in general.

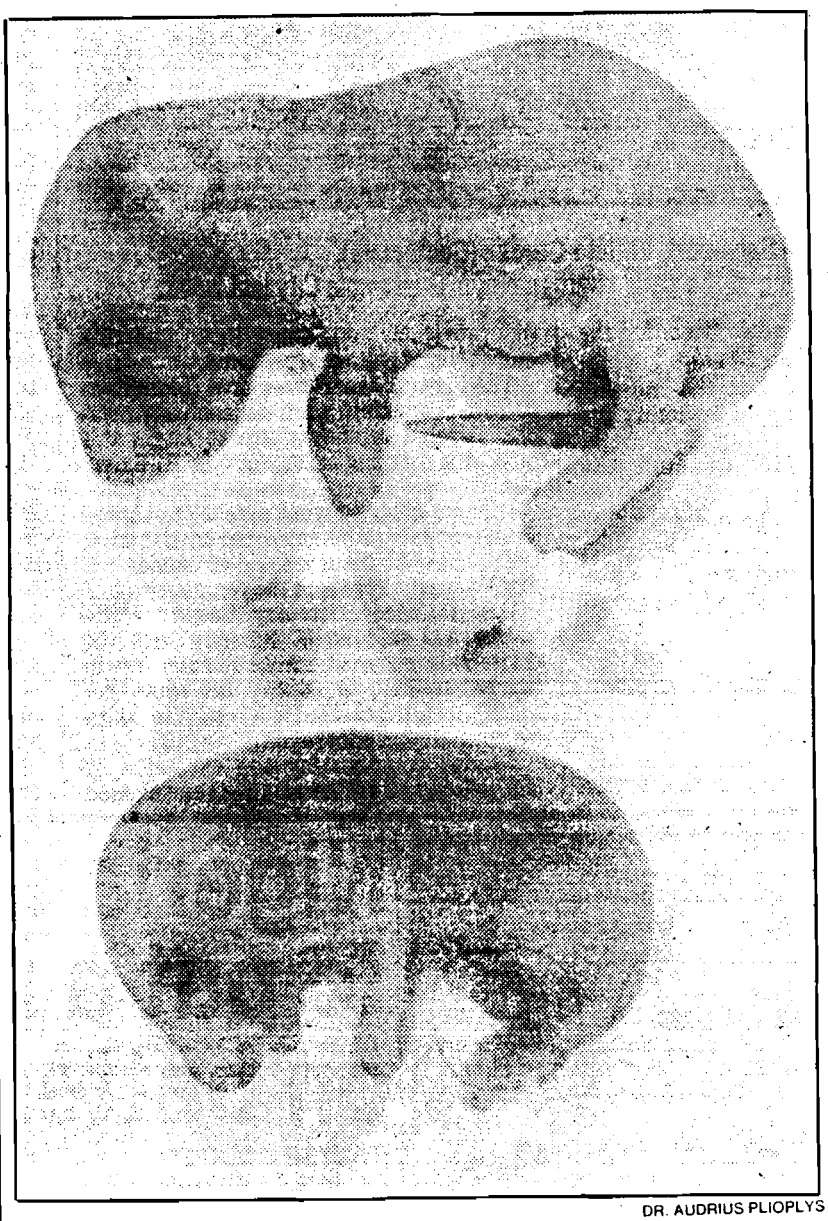
Dr. Plioplys cautioned that "much, much more research is necessary before any practical applications can be sought — Down's syndrome research is at the same stage that cancer research was decades ago."

Down's syndrome children usually have sloping foreheads, oriental-looking eyes, flat noses, low-set ears, generally dwarfed physiques and are mentally retarded. They also sometimes have malformed hearts. The condition is caused by the presence of an extra or third chromosome 21.

The condition is known as Trisomy Down's 21, because of the third chromosome. Normal people have 23 pairs of chromosomes that contain all of the genetic coding for that individual. It is also well established that almost all Down's individuals who live to be older than 40 develop the brain pathology of Alzheimer's disease. Researchers are convinced that many cases of Alzheimer's are genetic in origin and are linked to the 21st chromosome.

The research in Toronto "is very promising," in the opinion of Mary Coleman, a noted Washington neurologist and world-renowned expert on Down's and autism. The early results are appearing in scientific journals and will be presented at the Society for Neuroscience meeting in New Orleans in the fall.

Initial efforts at Surrey Place to explain the severity of retardation in Down's were started by Brian Scott, a neurobiologist, in collabora-



DR. AUDRIUS PLIOPLYS

Fetus of "Down's" mouse (at bottom) differs markedly from that of a normal mouse at top. Researchers believe similarities between "Down's" mouse brain cells and those of humans with Down's means they can use the mouse as an animal model to test out drug therapies.

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tion with doctors Ted Petit and Larry Becker, both of the University of Toronto. Dr. Scott and his colleagues have looked at the electrical properties of Down's neurons obtained from humans.

The electrical activity of a neuron is dependent on the flow of sodium and potassium through the cell membrane. This permeability defines the shape of the action potential or the basic functioning of the neuronal signals. Dr. Scott's results suggest there is an increase in the resistance of the cell membrane in Down's resulting in a decrease in the flow of potassium. This affects the basic functioning of the signals of the nervous system with sufficient magnitude to be the neurobiological basis for retardation, he contends.

Dr. Scott also has found that several similar changes occur in normal-aged neurons, which is significant because of the relationship between Down's and Alzheimer's. The hypothesis being put forward by some researchers is that the changes in the cell membrane result from the oxidation of unsaturated fatty acids and cholesterol.

This oxidation occurs in the normal human brain, but probably takes place more readily in the Down's brain because of the extra chromosome 21, they believe. This chromosome contains an enzyme called superoxide dismutase, or SOD-1, which is involved with oxidation. Because Down's individuals have more of this enzyme, more oxidation likely is taking place.

If researchers know the extent of these ionic disturbances in the cell membrane, the possibility exists for correcting the changes with drugs, Dr. Scott said. This would have a considerable effect in correcting the problems of aging and Alzheimer's, he believes. Dr. Scott intends to continue investigating these electrical abnormalities in greater detail, but will be using a mouse model of Down's syndrome supplied by Dr. Plioplys' laboratory.

Dr. Plioplys is taking the approach that the basic cause of retardation in Down's and the pathologies of Alzheimer's result from abnormalities in the cytoskeleton of the nerve cells in the brain. The cytoskeleton, like the skeleton of the body, provides the nerve cell with its structure and basic integrity. In addition, it is important in transporting nutrients and neurotransmitters throughout the body of the neuron. If there is a problem with the cytoskeleton, then neuronal functioning will not be normal.

The cytoskeleton is composed of three categories of protein: microtubules, neurofilaments and microfilaments.

One study carried out by Dominic Pupura at the Albert Einstein College showed that in children who were retarded for unknown reasons, there were abnormalities in the arrangement of one of these proteins, the microtubules. In Down's individuals, other researchers have found abnormalities in dendrites, which are part of the connections between neurons.

Dr. Plioplys found that there appears to be an unusual development of neurofilaments in Down's brains. In addition, the axons also appear to be thicker. He suggests that all of these observed differences stem from the abnormal regulation of the cell cytoskeleton itself. If this is the case, then, in his opinion, that could not only produce retardation but also set the stage for the eventual appearance of Alzheimer's disease.

In the Down's brain, the pathology of Alzheimer's does not appear until much later in life; thus it may be that normal processes are being misregulated. Recent studies show that there is a misregulation of microtubule development in Alzheimer's.

Both Dr. Scott and Dr. Plioplys have had problems conducting their research because of difficulty in obtaining human autopsy material. However, they are now using a mouse model; chromosome 16 in a mouse contains a number of the genes found on a human chromosome 21. Since the beginning of this year, Derrick McFabe, a University of Toronto physiology student, has been working in Dr. Plioplys' lab breeding "trisomy 16" mice (comparable to Trisomy Down's 21).

Both the human Down's and the mouse Down's victims have smaller brains, neurotransmitter changes, similar cardiac defects, immune-system abnormalities, hand, limb and face defects, and problems of spontaneous abortion.

Nerve cells taken from the normal and Down's mice substantiate the findings with humans. These results, Dr. Plioplys says, are attributable to the presence of the extra chromosome and to cytoskeleton changes. Also, there are extra interferon receptors on this chromosome.

Although interferon is very important in combating viral infections and as a possible cancer treatment, it slows cell growth and cell motility and division, and rearranges the cytoskeletal components. The extra chromosome results in 50 per cent more interferon receptors. And when interferon is added to the cells, there is a tenfold increase in sensitivity — that is, a substantial slowing of cell growth, motility and division.

Dr. Plioplys plans to use the mouse model to test the effects of interferon on brain cells themselves. If he is correct about the impact of the extra interferon receptors, then there are a number of drugs that can be tested on the mouse to block the anti-viral state. It may be possible in the future to reverse the interferon effects along with the permeability problems demonstrated by Dr. Scott. And because Down's is linked to Alzheimer's, then very possibly a treatment may apply to that disease as well.