Alzheimer's Disease: A Disease with Significant Public Health Implications for Canada.

P.H. St George-Hyslop, The Canadian Club of Toronto, May 12, 1997

100 years ago the most significant causes of human morbidity and mortality were infectious disease. With the advent of public hygiene, vaccination, and anti-microbials the threat posed by infection has diminished considerably although not totally. Their place however was taken by increased in risks from malignancies and cardiovascular disease. However, during the past two or three decades some small progress has been made into these diseases, thus some cancers are now treatable and the death rate from myocardial infarction seems to be falling. Again though, as one dragon is slain another raises its perfidious head. The latest dragon is a constellation of diseases many of which appear to be akin to what one expects from simple wear and tear. They include diseases like osteoarthritis, osteoporois, cataracts, and most alarming of all, a series of ultimately fatal degenerative diseases of the nervous system including motor neuron disease, Parkinson disease and perhaps the epitome of all of these diseases of aging - Alzheimer Disease. It is upon the latter, that I will focus in the next few minutes. To date, effective treatments do not exists for most of these diseases, a fact largely stemming from our incomplete understanding of the mechanisms by which these diseases occur. What I will show you in the next few minutes though is that hope is on the horizon, and that modern science can address these diseases. In particular I will show you how the University of Toronto, in collaboration with the Alzheimer Association of Ontario has already made significant in roads.

Before I do that, let me just put the matter into perspective. As you may know Alzheimer disease is a disease of the human CNS, which manifests in late adult life with a series of progressive impairments in memory and in cognition. It's more than just loss of memory, it's loss of ability to think , to reason, to discuss, to emote. In other words those higher intellectual functions which differentiated us from other animals. Occasional lapses of memory or difficulty remembering the name of a colleague, are normal and not a sign of Alzheimer Disease. Initially at least, the other neurologic functions such as the ability to walk, breath etc. are intact. But eventually Alzheimer Disease does progress to the point here the patient is unable to care for themselves, becomes incontinent and then bed-ridden, and ultimately dies. The important thing to note is that AD is a debilitating and eventually fatal disease which kills the patient dead, as dead as the nastiest of cancers or AIDS does.

The scourge of this disease is threefold. First it robs the patient of the qualities we most treasure - our intellectual abilities. Second it does so at the end of life. Frequently therefore it robs a man or woman of the chance to enjoy the fruits of a life time of hard work, the joys of grandchildren etc. Thus this disease is not only a murderer, but it is also a thief. Finally, because it renders the patient totally dependent upon others, it also imposes tremendous burdens upon relatives who become the total caregivers.

Now, that description may strike you as bit of hyperbole. Let me firmly disabuse you of that here and now, in two ways.

First, Alzheimer's Disease is the fourth leading cause of death in Western countries. There are at least 300,00 Canadians with AD right now. There are 3,000,000 American etc. It affects anyone from the poorest of the poor, to the rich and famous like Rita Hayworth and Mrs Rockefeller. It has even affected arguably the most powerful man in the world Ronald Reagan, and it began to do so while he was President of the US. It knows no race or sex boundaries. It affects women and men; it affects people with yellow or red or black or white or brown skins alike.

Secondly, the cost of caring for AD is $3.9 billion/year in Canada, $500 billion in the US. Now those are clearly cold statistics which may not have much practical meaning. Put another way, one in five Canadians over the age of 70, and one in three Canadians over eighty will develop this disease.

If these statistics come as a surprise to you, the reason that you didn't know this is because until recently at least, AD was considered a shameful disease and carried labels like "senile" which in our gerontophobic culture is more a pejorative than a diagnosis. Furthermore, by the very nature of the disease, those affected are unable to mount political action campaigns to embarrass the PM into promising gobs of money for research, they are unable to get rich and powerful actresses to mount monster publicity campaigns, for them. And finally, because there are no treatments, and because support services for caregivers are rather meager, the fate for the affected is often to be cloistered in nursing homes and are therefore outside of the mainstream of society. Put more bluntly, what this all means is that the victims of Alzheimer

Disease are entirely dependent upon you and me to make sure that the best is done for them both in terms of finding treatments and in looking after them with respect and dignity until that treatment is found. In fact, if the only thing that you take away from this is that your help is needed, then I'm satisfied.

I've painted a pretty bleak picture! Fortunately, there is hope, and the community has already begun to put their shoulders to the wheel. For instance, several years ago, The University of Toronto, a group of private individuals led by Mark Tanz, Ted Sherman, and Lionel Schipper, and the Alzheimer Association of Ontario set up the Centre for Research into Neurodegenerative Diseases at the U of T. Into that shell organiuzation a group of five scientists with diverse interested were recruited ... protein chemists, geneticists, toxicologists, biochemists, neuropathologists etc.

This congruence of Canadian intellectual power led to some thinking, and we realized that there are probably several different causes of Alzheimer Disease. Thus it seemed likely that some cases of AD are purely environmental. It was also clear that there were some families in which the disease was unarguably inherited from one generation to the next as a genetic trait. It was also clear that there were some families were there were a few too many affected family members but it did not actually clearly inherit as a genetic trait suggesting that in these families there was probably a genetic risk factor which was exacerbated by some environmental agents.

This situation is exactly the same as the case for cancers and heart disease. Thus some people get heart disease because they eat bad diets, smoke too

much and don't exercise.... all environmental causes. Some people have defects in lipid metabolism genes and get heart disease from a purely genetic cause. Many people however have a family history of heart disease but the disease is not purely genetic since it may skip generations etc. Here it is likely that non-genetic risks for heart disease are added to genetic risks for heart disease to bring out a prior susceptibility. And the same may be true for Alzheimer Diseasae.

We have some weak clues about likely environmental provokers of AD. For instance there is some suspicion that Aluminium may somehow be involved - probably as a secondary effect. There is also some evidence that prior significant head injuries are more common in, but of course not uniquely related to AD. However, we realized that the recent advances in recombinant DNA technology (also known as biotechnology or reverse genetics) provided us with a unique and powerful tool to look into the subset of Alzheimer Disease which had a purely genetic cases. In other words we could use this technology to identity the gene defects causing the purely inherited forms of the disease. Once we identity the disease gene we can determine its normal function, we can see what effects mutations would have on that function, and we could follow the subsequent biochemical reactions that lead to AD. We could then put the defective gene into cultured cells and into laboratory animals to recreate the disease and use these models to refine our understanding and to identify likely agents in the environment which would impact this pathway and which would therefore also cause AD. Finally, based upon this knowledge of the biochemistry of the disease, we could design rational therapies to combat this disease.

Base upon this logic, in 1991 we set out to isolate a gene which causes the most aggressive form of the disease, where the disease begins at age 35-50 years. We reasoned that this gene controlled a very important and fundamental step in the biochemical pathway leading to Alzheimer degeneration. After some 4.5 years of backbreaking labour we found this gene, and a few months later we found a second very similar gene which was also mutated in some cases of early onset familial AD. This discovery, has three immediate implications ... two positive, one sobering. First, we can used this knowledge both at the bedside to help physicians in their diagnosis of these forms of AD and to prognosticate. Second, The ability to predict who is at high risk of AD has the potential benefit in that those at risk can be given a preventative tretament before irreversible damage has been done to the brain. However, it should also be noted that appropriate societal safegaurds must be invented to prevent this sort of infoirmation being used to discrimate and create a new class of "genetic" lepers in society. Finally, and more importantly though, we can use the Alzheimer suceptibility gene to gain an initial understanding how these mutations cause the disease and to creating an animal model which recapitulates some of the features of human disease....and these studies are well underway.

In conclusion then, we see that in the long term there is now much more optimism than there had been even just a few years ago. Obviously, the steps from here to a treatment will be technically very demanding, being carried out right at the cutting edge of biotechnology. Necessarily, the sophistication of this type of research means that it will be several years away and that it will

also be very expensive. ... operating scientific budgets at the CRND running at over $3 million per year. Most of that budget is of course dependent on the Medical Research Council of Canada, private philanthropy, and support from the Alzheimer Association of Ontario (and I am deliberately being very specific here in singling out the Alzheimer Association of Ontario and its member chapters),

Finally, while it will probably be a few years before truly effective rationally designed treatments become clinically available, there is also some hope that better symptomatic treatments will be come available based upon the current knowledge of the types of neurons that degenerate in AD. In particular, there are a number of compounds being tested by various pharmaceutical companies which attempt to replace acetyl choline in the brain of AD patients. Again, the CRND at the University, and the Memory Disorders Clinic at the Toronto Hospital are actively engaged in this type of clinical research and if you require more information, please feel free to contact us .