
Dementia: Facing the Epidemic

Alzheimer's Australia
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**Presentation by Professor Constantine Lyketsos
The National Press Club, Canberra**



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Foreword

In recent years an important part of Dementia Awareness Week has been to invite an eminent overseas speaker as the guest of Alzheimer's Australia to promote awareness of dementia in a series of public lectures across Australia. This has been made possible by funding from the Australian Government through the National Dementia Support Program and unconditional grants from Pfizer Australia.

This year, Alzheimer's Australia was very fortunate to have Professor Constantine Lyketsos as our guest speaker. For the first time, we arranged for our guest speaker to address the Press Club with a view to ensuring that even greater numbers of people have the opportunity to hear from one of the leading international authorities on dementia.

The speech is wide ranging in explaining the nature of dementia, what is known about the pathology of dementia, the therapeutic strategies being investigated by the researchers, the importance of early intervention and the delivery of quality dementia care.

After 25 years of dementia research, a lot more is now known about dementia. There are exciting possibilities in dementia research in identifying those people most at risk of dementia and the therapeutic strategies that would make early intervention and prevention possible.

The enduring message of the wide ranging presentation of Professor Lyketsos is for increased investment in dementia research to reduce the number of people with dementia.



Glenn Rees
Chief Executive Officer

September 2009

Professor Lykestos is an active clinician, teacher, and researcher, Dr. Lyketsos is The Elizabeth Plank Althouse Professor in Alzheimer's disease research, Vice Chair of Psychiatry at Johns Hopkins University, and Chair of Psychiatry, at Johns Hopkins Bayview. He also directs the Johns Hopkins Memory and Alzheimer's Treatment Center, which provides cutting edge care to large numbers of patients while facilitating the translational research mission for the field.

An expert in the care and treatment of patients with Alzheimer's and related dementias, he has carried out pioneering work regarding the epidemiology and treatment of neuropsychiatric features of Alzheimer disease. His team is developing biomarker methods to accelerate treatment development for Alzheimer's and designing and implementing innovative clinical trials for the treatment of Alzheimer's. He also leads efforts to ensure the provision of state of the art *Dementia Care* to people with dementia in their community or assisted living homes.

His clinical expertise has been recognized by citation as one of *America's Top Doctors* for several years and was recently cited as a *Best Doctor In America*. He has been honoured by election to membership of the American College of Psychiatrists, the American College of Neuropsychopharmacology, and as Distinguished Fellow of the American Psychiatric Association. Dr Lyketsos has authored over 250 publications, book chapters, and commentaries, and Guest Edited several Journal special issues. He is the co-author of *Practical Dementia Care* (with Peter Rabins and Cynthia Steele) and of *Psychiatric Aspects of Neurologic Diseases: Practical Approaches to Patient Care* (with Peter Rabins, John Lipsey, and Philip Slavney).

PRESENTATION BY CONSTANTINE LYKETSOS

AT THE CANBERRA PRESS CLUB

23 September 2009

FACING THE DEMENTIA EPIDEMIC

Thank you very much Ken (Randall, President of the National Press Club). It's my great pleasure to be here with you today.

I thank Alzheimer's Australia for their invitation and the Australian Government for the funding that makes it possible for me to visit Australia during Dementia Awareness Week.

I should acknowledge too, the unconditional grant that Pfizer provide every year to Alzheimer's Australia for their awareness activities.

Governments in the last century tackled polio, cancer, heart disease and HIV/AIDS with passion and commitment.

My message is simple. We need the same passion and commitment to resolve the enormous challenges that dementia poses for our health care systems and for our society.

Let's be clear. The dementia epidemic is upon us. The facts speak for themselves.

Earlier this week, Alzheimer's Disease International published the ***World Alzheimer's Report***.

It was estimated in that report that there are 35.6 million people with dementia today. The numbers will nearly double every 20 years to 65.7 million in 2030 and 115.4 million in 2050.

In other words, by the middle of this century the number of people with dementia worldwide will be five times the population of Australia today.

In Australia, we know that by the middle of the century there will be over 1 million Australians with dementia. There are over 250,000 Australians with dementia today.

The social and economic consequences of this increase will be extraordinary.

This is not simply because of the sheer numbers of people who will have dementia, but because dementia is one of the most disabling of all chronic non communicable diseases.

The brain diseases that cause dementia, such as Alzheimer's disease, develop decades before diagnosis. There will be millions of others with milder memory disorders or who are concerned about losing their memories.

Australia became the first country in the world in 2005 to make dementia a National Health Priority. It was an inspirational decision for the rest of us. But few others have since followed Australia's lead.

Why is it that dementia has not been the focus of greater attention at the international and national levels?

Perhaps it has seemed like tomorrow's problem. In fact, dementia is very much today's problem. It is a problem not only for our parents, but for us, for anyone who hopes to live a long life. If you live beyond 85 you will have a 1/3 chance of getting dementia, and another 1/3 chance of caring for someone with dementia.

Maybe it is because dementia does not seem to kill as quickly as cancer or heart. But of course, dementia is terminal.

Maybe it is because dementia predominantly affects the elderly, and if we are honest, perhaps ageism is an important factor in the neglect of dementia.

Maybe it is because dementia is regarded as an inevitable part of ageing. Well of course it is not.

Maybe researchers like myself have failed to get across the important advances in research and the prospects for new therapeutic interventions. Or, about the effectiveness of currently existing therapies in helping patients and their carers: we cannot yet cure, but we can treat.

I am not a social commentator, but I can tell you about the positives of how we can tackle the dementia epidemic based on the evidence.

Before I get into the detail of what I have to say to you, let me emphasize my main messages.

First, we are within reach – maybe 5-20 years – of therapeutic interventions that will modify or slow the progression and onset of dementia. With greater investment in dementia research, those interventions might be available even sooner.

Second, we need a greater effort in applying what we now know from our research about diagnosis and management of dementia.

Third, researchers have demonstrated the benefits of good dementia care, but knowledge translation to those delivering care has been all too slow.

Fourth, we know how to reduce the risk of dementia. How can we better inform the wider community about what they can do to reduce their risk of dementia?

In short, I have no doubt that with determination we can reduce the prevalence of dementia and improve the quality of dementia care.

Let me give you the evidence for my well grounded optimism. In doing so, I will

First, define what we mean by dementia.

Second, explain what we know about the causes of dementia.

Third, outline strategies for therapeutic interventions that may delay the onset of dementia or modify its progression.

Fourth, talk about the elements of good quality dementia care.

Lastly, emphasise the importance of dementia research.

So What is Dementia?

Dementia is a clinical syndrome used to describe the symptoms of a large group of conditions that result in a progressive decline cognition. People associate dementia with loss of memory, but there are many other consequences, including decline in reasoning, communication skills and the capacity to organise daily life.

Dementia is associated with what clinicians call Behavioural and Psychological Symptoms of Dementia (BPSD). These symptoms vary greatly with the individual, but at some time every individual with dementia will experience depression, psychosis, aggression, apathy, or wandering.

Dementia can be caused by over 100 different diseases that affect the brain. These include neurodegenerative diseases such as Alzheimer's, Parkinson's or untreated hypertension, which slowly erodes brain tissue.

In fact, most cases of dementia are the result of a mix of different brain diseases, each contributing to the patient's symptoms. We can say with confidence that Alzheimer's, together with vascular disease, account for well over 75% of all dementias.

While the main risk factor is age, dementia can affect those under 65. In Australia it is estimated that there are 15,000 people with younger onset dementia. The social and economic consequences for these young people, and their families, are particularly devastating.

Dementia can be distinguished from normal cognitive ageing through careful diagnostic evaluation by trained physicians. Dementia is usually preceded, sometimes over years, by mild memory loss or confusion but without affecting daily life in a major way. These precursor symptoms are known as mild cognitive impairment or MCI.

Dementia generally progresses over 5-8 years, sometimes as long as 20. Eventually patients with dementia become severely debilitated with little ability to communicate with their environment, verbally or otherwise. They typically become incontinent, unable to walk and require considerable effort to feed.

In the terminal stage which can last months, sometimes years, the patient is bed bound, non-verbal and totally dependent on others. Dementia accelerates death

through debilitation, by making its victim vulnerable to infection, aspiration and damaging falls, or through wasting away. In the United States as in Australia, dementia is estimated to be the fourth largest cause of death in older people.

The carers of people with dementia become isolated from their personal and social networks because they spend almost all their time supervising or caring, with precious few moments alone. Research has repeatedly shown that caring for someone with dementia is unlike any other carer experience.

Dementia care is more physically and emotionally overwhelming and as a consequence, it is more damaging to the carer's health. In some cases lethal for carers as well. We must never forget, therefore, that any serious effort to care for people with dementia must include care for the carers as a central component.

What Do We Know About The Pathology of Dementia?

While we do not fully understand the details, research over the past 25 years has given us a wealth of knowledge about the changes that take place in the brain with dementia. We now understand that dementia is characterised by changes to the brain that precede the clinical picture by years if not decades. Put another way, brain-damaging processes unfold in the brains of large numbers of people without symptoms for years. Treating these asymptomatic people is the eventual goal of dementia prevention.

There are interesting parallels with heart disease. We know that years of high cholesterol, smoking and related factors damage blood vessels. Introducing cholesterol or other therapies at a late stage to those who already have loss of heart muscle tissue and other problems is likely to be ineffective.

So too with dementia. Once an individual has started to lose significant numbers of brain cells, therapeutic interventions are less likely to be effective. The message is that we need to intervene early before the damage is too great.

Let me give you a more medical description. Two thirds of people with dementia have what we call the "Alzheimer's pathology" in their brains. This is a characteristic physical pattern in the brain consisting of amyloid plaques and neurofibrillary tangles around or within the nerve cells of the brain. In addition, tiny immune cells, known as the microglia, become highly active. These cells are normally responsible for "cleaning up" damaged tissue, but in Alzheimer's disease they seem to be associated with substantial neuronal loss. These hallmarks of Alzheimer's in the brain likely develop, as I have said, over a very long time.

Under the prevailing hypothesis – the *amyloid hypothesis* – researchers believe that this long process begins with the misprocessing of a protein. We all have the amyloid precursor protein or APP in our brains. But in Alzheimer's disease, the protein is misprocessed to produce a toxic protein fragment known as Abeta1-42.

Over time, through steady production, Abeta1-42 accumulates in plaques outside nerve cells. These are the amyloid plaques we see under the microscope. Over time Abeta1-42 erodes the synaptic connections between the nerve cells and ultimately

kills them. How this happens is not clear. Possibly our immune system activates the microglia which, in their frustrated efforts to clear the plaques, produce large amounts of inflammatory chemicals near synapses that are also toxic.

As the synapses that connect different nerve cells slowly disconnect, chemical communication between nerve cells in the brain falters, leading to symptoms. The function of nerve cells is to communicate. A disconnected nerve cell activates a "self-destruct" signal, leading to neuronal death, or apoptosis. In the process of dying, neurofibrillary tangles appear. Although poorly understood, it is likely that very important, secondary mechanisms become activated and the process spreads through the brain.

This spread through the brain follows a predictable pattern. The cortex, or rational thinking part of the brain, is involved at first, eventually affecting cells that project from cortex into the deeper sub cortical areas. The most vulnerable part of cortex, the area which dies first, is the hippocampus which is central for memory. The dying process involves several neuro-transmitter systems, such as those that make serotonin, dopamine, and norepinephrine. The loss on these latter systems has significant consequences for the behavioural and psychological symptoms of dementia.

The particular symptoms a patient suffers depends upon *the location of the brain damage*. Patients with different causes of dementia may have similar symptoms because different diseases affect the same parts of the brain. Patients with Alzheimer's and Pick's Disease both have memory loss, disinhibited behaviours, sleep disturbance, etc., if their particular disease happens to hit the relevant brain areas and systems.

What Are The Possible Therapeutic Strategies?

The excitement of dementia research is that the evidence base generated in the last 25 years has enabled us to identify a number of strategies that offer hope for the treatment of dementia. Broadly speaking, these strategies fall into three categories:

1. Prevention or removal of amyloid formation (particular to the treatment of Alzheimer's disease) using new compounds such as beta and gamma secretase inhibitors, and vaccination.
2. Modulation of known risk factors including lowering blood pressure, reducing oxidative stress or inflammation, and stroke prevention.
3. Increasing growth of connections between brain cells or growing new brain cells to replace those lost, using nerve growth factors, stem cells and drugs that increase neurogenesis.

In the case of Alzheimer's disease, much of the recent focus has been on the biology of amyloid as a treatment target.

Since the toxic amyloid form of Abeta1-42 is made through misprocessing of APP by beta and gamma secretases, several pharmaceutical companies have developed beta and gamma secretase inhibitor medications that have progressed to human therapeutic trials.

Another line of treatments has emerged from the understanding antibodies can clear the amyloid within the plaques from the brain. This has been shown repeatedly in mouse models of Alzheimer's amyloid.

Medications for all of these strategies are in clinical trials. For all these approaches significant caution is necessary because of unknown safety concerns. For example, inhibiting beta and gamma secretases may run severe, yet unknown, risks since these enzymes have functions beyond the processing of APP. An early study of active immunotherapy years ago led to evidence that amyloid was cleared from the brain, but also to serious untoward effects that caused encephalitis, a brain inflammation, and death in about a dozen research participants with Alzheimer's.

While these anti-amyloid therapies appear exciting, it is very important that we remain cautious. We will be testing the amyloid hypothesis over the next decade. But we will be testing *one aspect of it*, namely that clearing amyloid in people with dementia can reverse symptoms. As with the heart disease example this is not too different from reducing cholesterol in somebody with heart failure. In the case of dementia the brain damage may simply be too much to be reversed. A sobering study followed people from the first vaccination study and reported that those who died did not have much amyloid but died with advanced Alzheimer like dementia.

The second strategy I referred to involves modulating factors such as high blood pressure, high cholesterol, oxidative stress, and inflammation, which we know are associated with the progression of dementia in the brain. Many medications involving these mechanisms have not been found helpful in people with dementia. Nevertheless, these treatments may help delay onset of dementia. Consequently, efforts are underway, involving medications, dietary change, exercise, and mental stimulation to examine the preventive value of these strategies.

In the meantime, while we cannot do much about ageing or our genetic makeup, we can do something about our lifestyle. There is good evidence that physical, mental and social activity together with good nutrition will assist some to reduce their risk of dementia. While there is no guarantee that if you do all the right things you will avoid dementia, lifestyle changes will undoubtedly benefit some. And it will help physical health as well as brain health, and is a course of action that can do no harm.

Until new therapeutic interventions are available, those concerned with public health should be encouraging people of all ages, and particularly those in their forties and fifties to reduce their risk of dementia through public education activities such as the **Mind Your Mind**® Program developed by Alzheimer's Australia. It is cheap at any price compared with the cost of dementia both economic and social.

Lastly, I mentioned strategies to keep injured nerve cells from dying or to use stem cells. Research in this area is in its infancy and considered by many as "high risk—high pay off" as it may alter more fundamental disease mechanism. Substances have been identified that are natural nerve growth factors or otherwise "neuroprotective." Delivering these to the slowly dying dementia brain, at the right time, will prove to be an enormous challenge but may produce huge payoffs. Substances which are neuroprotective in the test tube, however, have not been helpful if delivered in pill form to patients with dementia. Perhaps delivery into the brain by neurosurgical

means will be more effective—a trial is already starting in the US of a nerve growth factor injected directly into the hippocampus of people with Alzheimer's dementia.

Regarding stem cells, many researchers are sceptical of these technologies. But the job of the researcher and clinician is to be interested in all possibilities. There is some evidence in mouse studies that stem cells may hold out promise. The hope is that we may be able to use stem cells to replace multiple cell types thus patching broken connections over parts of damaged brains. Scientists in Australia at the University of New South Wales, the Queensland Brain Institute and at the Monash Immunology and Stem Cell Laboratory are in the forefront of brain stem cell research, both in the development of new types of stem cells and also in testing them in brain disease.

The Importance of Early Intervention

The great challenge for us is how are we going to target and treat people in the early phases of the brain disease when there are no symptoms? Imagine a cascade that begins with amyloid and its processing, followed by deposition of plaques, synaptic disconnection, injury to neurons, tangle formation, death of neurons and death of neuronal systems leading to symptoms. We need to develop measures for each part of this cascade in living people.

There is recognition of the importance of these issues in the research effort being made to identify significant biomarkers that measure each part of the cascade. For example, we now have the ability to measure the deposition of amyloid in the brain using PET with two radio labelled molecules.

We are close to using PET radio labelled molecules to image activation of the brain's immune system. Similarly we can measure accurately levels of amyloid and other characteristic features like tau protein in cerebrospinal fluid obtained through a spinal tap – a routine procedure that is increasingly becoming part of the research and care of people with dementia.

MRI brain imaging methods are being used to quantify the loss of structure and function in key parts of the brain, and may be directly able to image amyloid plaques.

Blood tests are also being developed. At Johns Hopkins we are developing blood measures of lipids that might spill out of the brain as nerve cell membranes die off.

Very soon, we will be able to place a person in a single scanner for 2 hours to get an MRI and two PET scans measuring amyloid or microglia activation. This coupled with cerebrospinal fluid and blood tests will allow us to stage the process in anybody at risk, with signs of early mild cognitive impairment, or with dementia. By repeating these procedures we will be able to estimate the speed at which the process is evolving in any individual.

The HIV-AIDS field was revolutionized by the ability to measure viral load and count the CD4 receptor cells. Very soon we will have similar advances in the Alzheimer's field allowing us to quantify the biological signature of the disease in individuals. Through this we will be better able to target treatments at stages when they are most

