

## Preventing and Treating Alzheimer's Disease and other Dementias

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*Thanks to the work of charities such as Alzheimer's Research UK and the Alzheimer's Society, coupled with good political leadership, Britain is today playing a leading role in finding the causes of neurodegenerative diseases and developing new ways of preventing their onset and slowing their progression.*

*Provided adequate investment in well-directed, socially as well as bio-scientifically informed, University and pharmaceutical industry research can be sustained, innovative medicines will in and after the 2020s reduce the number of people living with dementia. But to fully meet the Prime Minister's Challenge on Dementia, England also needs to further modernise its approach to providing equitably funded and well-coordinated health and social care for people living with Alzheimer's Disease (AD) and related disorders.*

*There is evidence that the long-standing NHS and social care funding divide has undermined the quality and scope of health services and distorted social care. It may also have caused the unfair financial penalisation of individuals and families affected by conditions such as AD. There is a growing need for reform aimed at better meeting the public's 21st century health care requirements.*

Across the world, in rich and poor nations alike, life expectancy at birth has increased by 30 years over the course of the last hundred years. This progress – based mainly on reductions in infectious disease deaths, followed in wealthier countries by major improvements in the prevention and treatment of vascular events such as strokes and myocardial infarctions (heart attacks) – has been associated with reductions in age-specific disability rates. As people live longer they normally become healthier at any given age, and stay independent for longer. This is one of the reasons why political and other commentators are mistaken if they blame 'population ageing' for being the main cause of rising health and social care costs (De la Maidonneuve and Martins, 2013), or say that further improving the effectiveness of publicly funded services like the NHS could make them unaffordable.

Increasing clinical and allied care labour costs are normally the largest single reason why service spending rises as societies develop and become richer. However, it is true that longer average life expectancies coupled with low birth rates change the nature of health and social care demands. Addressing the burdens of lost life and lost years of independence and fully enjoyable existence caused by conditions such as Alzheimer's Disease and Parkinson's Disease becomes progressively more important in modern societies, as does cancer prevention and treatment. Investing more in both these areas should be seen as a hallmark of informed health related priority setting.

There is now evidence that better health at every stage of life, from being well-fed and otherwise protected from harm *in utero* and immediately after birth to being mentally and physically active and free from problems like smoking, high blood pressure and type 2 diabetes in middle age and beyond can delay the onset, and even prevent the

symptomatic occurrence, of at least some forms of dementia. Yet to minimise its personal and financial costs to individuals, families and communities, much more needs to be achieved in the fields of neurodegenerative disease prevention, treatment and care.

Against this background and that of Professor John Hardy's January 2016 UCL School of Pharmacy lecture '*Pathways to Neurodegeneration*' (see Box, page 2) this UCL School of Pharmacy *Briefing* summarises evidence from recent research in areas ranging from human genetics and epidemiology to the economics and sociology of health and social care. Its focus is on Alzheimer's Disease and issues relating to dementia as opposed to other forms of neurological disease.

Key messages range from the need to improve the equitable provision of affordable and well-coordinated health and social care for people and families affected by dementias to the long-term importance of sustaining research into the causes of neurodegeneration and its prevention and treatment throughout the 2020s and in subsequent decades. This will require not only charitable and direct government support, but also the establishment of viable commercial markets for the supply of incrementally improving disease inhibiting treatments.

This UCL School of Pharmacy *Media Briefing* also discusses the role of pharmacy with that of the other health professions in improving the quality of health and social care. However, it begins with a brief overview of the steps taken by the 2010-15 coalition government and the present Conservative administration led by David Cameron to make Britain both a world-leading centre for neurodegenerative disease research and '*the best country in the world for dementia care and support*' (David Cameron in Department of Health, 2015).

**Professor John Hardy** is a geneticist and molecular biologist. He began his work on Alzheimer's Disease and other neurodegenerative conditions in Sweden at the start of the 1980s. He subsequently worked in Imperial College and then in settings such as the Mayo Clinic in the US, before becoming Professor of Neuroscience at UCL in 2000. Professor Hardy recently won the \$3 million Breakthrough Prize in Life Sciences for his research into the causes of Alzheimer's Disease, Parkinson's Disease and frontotemporal dementia. Previously, he has received other important awards for his Alzheimer's Disease research and the discovery of a key mutation in the amyloid protein precursor gene in 1991 – see main text. John Hardy was elected a Fellow of the Royal Society in 2009. On January 12th 2016 he will give the UCL School of Pharmacy New Year lecture at the Royal Society, entitled *Pathways to Neurodegeneration*.

## The Prime Minister's Challenge

The Prime Minister's Challenge on Dementia was first launched in March 2012, about a year before Margaret Thatcher died from what has been reported to have been 'vascular dementia'. An updated *Challenge on Dementia 2020* pledging more than £300 million for funding into dementia research in the five year period to 2020 was published in 2015.

Related commitments include opening an International Dementia Unit and enhancing staff NHS training, as well as measures ranging from improving care metrics to increasing the numbers of people with dementia who participate in research studies. The extended policy document also indicated that Britain will seek to follow Japan in creating 'dementia friendly' cities and institutions, through increasing awareness and understanding of the needs of people living with reduced cognitive capabilities.

Other recent policy linked initiatives (which were in large part inspired by the efforts of bodies such as the Alzheimer's Society and Alzheimer's Research UK – ARUK) involve:

- **Establishing an International Dementia Discovery Fund (DDF).** At the G8/G7 'Dementia Summit' in December 2013 the UK and the US commenced a search for new opportunities for enhanced international collaboration on dementia research, with the goal of identifying a 'cure' or effective disease modifying therapy by 2025.<sup>1</sup> In March 2015 a \$100 million global Dementia Discovery Fund was unveiled by England's Secretary of State for Health, Jeremy Hunt. This included, over and above their 'in-house' research investment programmes, donations from the pharmaceutical companies GSK, Johnson and Johnson, Eli Lilly, Pfizer and Takeda, as well as contributions from the Department of Health and Alzheimer's Research UK.<sup>2</sup>

1 The creation of a World Dementia Council was one of the actions agreed at the G8/G7 summit in December 2013. The Council aims to within the next few decades stimulate innovation, development and the commercialisation of drug and other forms of treatment and care.

2 Alzheimer's Research UK has additionally pledged £100 million to dementia research over the next five years via their Defeat Dementia campaign, and has initiated a £2 million collaborative venture between the Gurdon Institute, the University of Cambridge and UCL in order to form a Stem Cell Research Centre.

- **The Dementia Platform UK (DPUK).** In October 2014 the Chancellor, George Osborne announced £37 million funding as part of the Clinical Research Infrastructure Initiative. This has resulted in a multimillion pound public-private partnership led by the Medical Research Council (MRC). It is creating three new national networks for imaging, informatics and cell biology. It is also seeking to consolidate into one managed entity the world's largest study population for work in dementia research, involving two million people aged 50 or over drawn from 22 existing study groups in the UK.
- **Funding the Drug Discovery Alliance (DDA).** Building on the experiences of similar initiatives taken by cancer charities over the last 20 years, ARUK announced in February 2015 the development of three flagship Drug Discovery Institutes, based at the Universities of Cambridge and Oxford and in University College London (UCL). Each is receiving £10 million. Ninety research scientists are being employed in high quality facilities in an attempt to fast track the development of new treatments for AD and associated conditions.
- **The Dementia Research Leaders Programme.** For the UK to remain a world leader in dementia research the nation must maintain a relevant skill base and ensure that there are sufficient incentives to keep dementia researchers within the field. The Alzheimer's Society has therefore developed a Dementia Research Leaders Programme. Following an initial investment of £6.5 million DRLP has supported 75 dementia researchers in the 18 months to October 2015.
- **Creating a National Dementia Institute.** Following the 2015 Comprehensive Spending Review, November 2015 saw the announcement of a further £150 million of new funding (to be made available over 5-10 years) for a national Dementia Research Institute. Without duplicating other work, this will seek to act as a UK hub to drive forward the search for more effective preventive and therapeutic interventions in informed and well-coordinated ways. In January 2016 the MRC, which is charged with leading the creation of the new Institute, will open a competitive process aimed at identifying the University best placed to host such a body.

Such developments mean that Britain is now spending some £60-70 million (in the order of \$US 100 million) on publicly and charitably supported dementia research. Although limited in comparison to the US input of over \$500 million, Britain (as is also so in the cancer research context) is funding about a tenth of the global public neurodegenerative disease research effort, despite the fact that UK GDP is only 4 per cent of Gross World Product. The available evidence also indicates that research undertaken in settings such as the leading UK Universities and the NHS is of high quality and can be unusually productive in global terms.

## Defining Dementia

Up until the closing decades of the nineteenth century the term dementia was commonly used to refer to a state of 'madness', which could be taken to mean virtually any form of imprecisely defined psychiatric disturbance. It was often assumed that losing mental capacities such as short-term memory and becoming more easily confused or 'lost' was a part of normal ageing.

However, at the start of the twentieth century the pioneering German researchers and clinicians Alois Alzheimer and Emil Kraepelin offered the first description of what has worldwide become known as Alzheimer's Disease. After the death of a patient called Auguste Deter in 1906 they examined her brain, and noted that it had suffered shrinkage and had within it abnormal deposits now often referred to as 'amyloid plaques' and neurofibrillary tangles (NFTs).

The subsequent hundred years have seen the step-by-step development of modern neuroscience (see, for example, Glickstein, 2014) and the introduction of progressively more sophisticated approaches to the diagnosis and categorisation of dementias and other neurodegenerative conditions. Alzheimer's Disease (AD)<sup>3</sup> accounts for around two thirds of all cases of broadly defined dementia. In addition to memory loss, AD can be accompanied by symptoms such as mood swings and behavioural disturbances. Other types of dementia include vascular dementia (associated with multiple small strokes and allied events), dementia with Lewy bodies (which has close links with Parkinson's Disease, and is characterised by atypical alpha-synuclein and ubiquitin protein deposits in the brain) and frontotemporal dementia (FTD).

The latter was first described in the late nineteenth century. It involves a selective loss of neurones in the frontal and/or temporal lobes. The condition that recently caused the death of the author Sir Terry Pratchett is posterior cortical atrophy (PCA) which was first identified in the 1980s. The fundamental nature of neurodegenerative disorders is not as yet fully understood, and there may well be complex interactions between factors such as vascular pathologies and the development of disorders like Alzheimer's Disease.

Because of this lack of detailed insight, neurodegenerative disease research can currently be said to be between 10 and 20 years behind cancer research, where the fundamental biology is now better understood. However, with continuing research investment brain functioning will be more comprehensively described, and the precise causes of phenomena like selective neuronal cell death revealed. This will in turn create additional preventive and disease treatment 'target' opportunities.

A second key point is that the loss of cognitive abilities seen in dementia is now known not to be a part of normal ageing. Brain functioning changes as people live into their 70s, 80s and 90s, in part because of normal neuronal loss

<sup>3</sup> Alzheimer's Disease can be divided into Early-Onset and Late-Onset (EOAD and LOAD) forms, in addition to which there are a variety of rare familial forms of dementia associated with single gene variations

and because they have more experience to draw on than younger individuals. Yet healthy, active ageing does not involve the sorts of disability seen in contexts like those of Alzheimer's Disease and Parkinson's Disease. This is important, not least in the context of assuring appropriate access to good quality, equitably funded, health and social services. Dementia is a form of illness like cancer or a heart attack, and deserves similar levels of publicly supported care delivered proportionately to needs.

## The Disease Burden

Amongst individuals aged 65-69 around 2 per cent are presently living with a form of dementia. In people aged 85-89 this proportion is about 20 per cent. This is why the prevalence of dementia is higher in 'older' populations.

Nevertheless, there is also evidence that age specific rates of dementia have in the UK fallen by about 20 per cent since the start of the 1990s (Wu et al, 2015). This is likely to be due to the improvements in living conditions experienced by more recent generations, coupled with factors such as improved vascular health and the increasing proportion of the population involved in 'mental labour'. It appears that intellectual activities help people to build up 'mental reserves'. This may enable them to preserve normal performance for an extended period, even in the presence of underlying progressive disease.

At the population level it is uncertain whether people currently in their 50s and 60s who have high (but increasingly well treated) diagnosed rates of type II diabetes will go on enjoying reducing age specific rates of dementia. Yet for individuals actions such as stopping smoking and reducing blood pressure levels are clearly protective. Across the UK about 800,000 people are presently living with some form of dementia. Of this total around half a million have Alzheimer's Disease. Without new preventive treatments or more effective public health programmes there will be around 1 million UK citizens living with dementias in 2025, and approaching 2 million by the start of the 2050s.

Because people with disabilities due to conditions such as Alzheimer's Disease often live for many years (for those aged 65 at the time of diagnosis mean survival is roughly 8 years) the care costs incurred are high compared with most other forms of physical illness. Current UK estimates are in excess of £25 billion a year, over half of which are met via the contributions of unpaid carers or as a result of privately purchased nursing home costs (Alzheimer's Society, 2014). Suggestions that families alone should do more to meet the societal costs of dementia may on occasions be based on an inadequate understanding of this reality.

The annual cost of dementia care to the NHS and Local Authorities in the UK is estimated to be around £9 billion a year, or about 6 per cent of combined health and health related social care costs. Such figures highlight the fact that although providing good quality publicly funded universal health and social care to people living with dementia should from a national perspective be seen as eminently affordable,

both now and in the future, the costs incurred by individuals and families can in all but the most advanced social systems sometimes be catastrophic.

Even when care costs are less challenging they still can be high, despite standards being variable. More effective preventive and/or ameliorative treatments will offer not only reduced personal distress, but also substantive financial savings.

## Research Challenges

Until recently the effects of neurodegenerative diseases on the brain could only be examined by autopsy – that is, *post mortem*. This made diagnosing them and investigating their causes uniquely difficult. The fact that – as is now known because of the work of scientists such as UCL's Professor Nick Fox – conditions such as Alzheimer's Disease can take decades to develop has further amplified the research challenges involved.

As a result of such barriers much research has to date concentrated on families known to carry relatively rare genetic variations associated with early onset forms of dementia. One of the best-known of these affects 5000 members of an extended family in Antioquia, in north-western Colombia.<sup>4</sup> About a third of these individuals have a harmful mutation in a gene called presenilin 1 (PSEN1 – presenilin mutations affect the synthesis of beta amyloid, as described below). This causes them to develop Alzheimer's Disease at an early age.

However, in addition to increasingly rapid and accurate methods for identifying genetic associations with disease and conducting psychological assessments of individual's changing cognitive abilities through life, technologies such as functional Magnetic Resonance Imaging (fMRI) now offer researchers new ways of observing the living brain.<sup>5</sup> This is helping to drive advances in understanding the working of healthy brains, and of the pathological build-up of Amyloid beta (A $\beta$ ) and Tau protein.

## The Biological Basis of Alzheimer's Disease and other Neurodegenerative Disorders

In the 1970s dementia research was still in its infancy. Bio-medical scientists had little knowledge of the molecular basis of the diseases involved, and the research being undertaken was not well organised. However, this situation began to change when in the early 1980s it was observed that there is an association between Down's Syndrome (a form of learning difficulty caused by trisomy 21 – having three copies of chromosome 21 per cell – which invariably leads to early onset dementia, typically at around the age of 50)

4 Journalists interested in this field may wish to investigate the work of the Alzheimer's Prevention Initiative

5 Such imaging technologies are also opening the way to the improved diagnosis and more timely treatment of multiple sclerosis, which affects over 100,000 relatively young people in the UK

and familial AD.<sup>6</sup> The realisation that both conditions were associated with raised levels of A $\beta$  led to the cloning of the amyloid precursor protein (*APP*) gene and its localisation to chromosome 21 in 1987.

The work of John Hardy and his colleagues meant that by 1991 a mutation in the *APP* gene, which leads to a build-up of A $\beta$  in the form of amyloid plaques in the brains of affected individuals, was found to be associated with familial AD (Goate *et al.* 1991). It was this work that put *APP* and A $\beta$  at the forefront of modern theories about AD pathogenesis.

Amyloid beta can be said to be a breakdown product created by the cleavage of the amyloid precursor protein by enzymes called beta secretase and gamma secretase. A $\beta$ 's normal function is not well understood, although its possible roles include the activation of kinase enzymes; protection against oxidative stress; regulation of cholesterol transport in the brain; anti-microbial actions (A $\beta$  has a pro-inflammatory activity); and helping in the transcription of DNA into RNA.

There are two types of amyloid beta: A $\beta$ 40, which normally accounts for 90 per cent or more of all A $\beta$ , and A $\beta$ 42. The extra 2 amino acid subunits present in A $\beta$ 42 cause it to be prone to adopting a unique three-dimensional shape that results in its clumping together to form insoluble aggregates. In the brains of people with Alzheimer's Disease the ratio of A $\beta$ 42 to A $\beta$ 40 is increased, making it easier for so-called 'senile plaques' to form.

The basic amyloid hypothesis posits that it is the plaques formed when A $\beta$  clumps together that are responsible for the clinical symptoms of AD. It may be that A $\beta$  damages and kills neurones by generating reactive oxygen species during the process of self-aggregation. As a result the functioning of glucose and glutamate transporters could be impaired and a variety of other phenomena triggered. These events interfere with synaptic transmission (the passage of signals between brain cells) and eventually lead to neurone death.

In the early stages of the condition plaques first begin to form in the areas of the brain involved in learning, memory, thinking and planning. At this point they appear to be particularly damaging to the 'cholinergic neurones' (nerve cells which mainly use the neurotransmitter acetylcholine – Ach – to send messages) that link cortical structures with other parts of the brain. But as the disease progresses plaques spread to the brain areas involved in speaking and understanding speech, and in movement and spatial positioning. Towards the end stage of the illness most of the cortex has been damaged, and there is significant brain shrinkage due to widespread cell death.

There is no doubt that abnormal A $\beta$  deposition is involved in the occurrence of AD. But even so, the amyloid hypothesis is not conclusively established. Some evidence suggests that the plaques are not the primary cause of AD as they can be found in cognitively normal adults, and plaque burden is not well correlated with observed levels of cognitive deficit.

6 Early onset AD is a hereditary condition marked by onset of clinical symptoms, typically before the age of 65

An amended hypothesis is based on the idea that the most damaging form of A $\beta$  involves a lower number of molecules than that found in larger plaques (McDonald *et al.* 2010). These small, soluble ‘oligomers’ (in effect, limited size polymers) may block cell-to-cell signalling at synapses and activate immune system cells that trigger inflammation and destroy disabled cells. Amyloid beta oligomers may also act as prions (atypically folded proteins which serve as tiny infectious particles) or ‘seeds’ that trigger additional A $\beta$  miss-folding in a cumulatively destructive chain of events.

A second process that is believed to drive AD in its later stages is the intracellular accumulation of the Tau protein. Tau aggregates abnormally as pairs of helical filaments which interfere with normal cellular functions. As a result, axonal transport is impaired, affecting the nutrition of axon terminals and dendrites. These Tau protein aggregates, known as neurofibrillary tangles (NFTs), are thought to be a form of secondary lesion in AD, with amyloid plaque formation as the primary lesion.<sup>7</sup>

Although Tau build-up can be found in early AD, it is generally well-correlated with the clinical stages of the disease. NFTs initially form in the areas of the brain important for memory, before progressing to other areas. To date, no mutations in the Tau gene have been associated with AD. But such mutations have been associated with frontotemporal lobe dementia (Hutton *et al.* 1998).

## Additional Theories

Another important concept linked to the amyloid hypothesis is that impaired clearance of A $\beta$  can result in AD. This is suggested by that fact that A $\beta$  brain clearance is reduced by a third in cases of sporadic AD compared to controls, whilst production of A $\beta$  remains normal.

The brain, like the eye, is not (overtly) connected to the lymph system. In healthy individuals perivascular drainage along the cerebrovascular basement membranes (CVBM) is one of the mechanisms by which A $\beta$  is removed. However, in some older people’s brains changes in the composition and structure of the CVBM may contribute to the accumulation of Amyloid beta in the walls of cerebral blood vessels, a phenomenon observed in the majority of AD cases. It has been suggested that (especially in more atherogenic social environments) as human cerebral arteries age ‘stiffening’ of the vessel walls reduces the amplitude of the pulsations responsible for the drainage of A $\beta$ , and so gradually leads to a pathological build-up of the protein/peptide (Morris *et al.* 2014).

The fact that many families with hereditary forms of AD do not possess any mutation in the *APP* gene demonstrates that AD is aetiologically heterogeneous. Additional research has identified the *PSEN1* (presenilin-1) and *PSEN2* (presenilin-2) genes<sup>8</sup> as having a role in autosomal

7 There is limited evidence that misfolded A $\beta$  can induce Tau to miss-fold and form tangles.

8 These genes are involved in the regulation of a range of proteolytic events, including the breakdown of gamma secretase. As a result they can play an important role in the generation and/or accumulation of A $\beta$ .

dominant (conditions in which a mutated gene from just one parent is sufficient for the disease to be manifested) versions of familial AD (Sherrington *et al.* 1995). *APP*, *PSEN1* and *PSEN2* variations make up the only fully penetrant (disease causing in all subjects inheriting the genes) mutations to date known to be involved in AD.

In addition, family and other studies have revealed that the relatively common E4 allele of *APOE* (Apolipoprotein E) is associated with a markedly increased AD risk (Saunders *et al.* 1993),<sup>9</sup> especially in women in later life. As the Figure below illustrates, apolipoproteins are involved in clearing A $\beta$  from the brain. However, although *APOE 4* is clearly important in the AD context awareness of this has not as yet led to any specific form of treatment development.

More recently variants in *TREM2*, the product of which has an anti-inflammatory role, were identified as causing increased susceptibility to late onset AD (Guerreiro *et al.* 2013b; Jonsson *et al.* 2013). Late onset Alzheimer’s Disease (LOAD – defined as occurring when symptoms begin after the age of 65) is the most common form of the disease.

Unlike the case with familial AD, it has proved hard to identify clear lines of genetic causation in LOAD. Even so, researchers now believe that people inherit 60-80 per cent of their risk for late-onset AD, with the remainder being environmentally determined. The development of polygenic models is now underway in order to establish ways of determining more accurately who will develop AD.

Genome-wide association studies have led to the identification of over 20 genetic loci with low risk effects for AD. The genes implicated include, among others, *BIN1*, *CLU*, *CR1* and *SORL1*. They are involved in areas such as the functioning of the immune complement system, inflammatory responses and brain cholesterol/lipid metabolism (Guerreiro *et al.* 2013a). Pathways like those relating to cholesterol modulation in the brain may now offer targets for novel drug therapies.

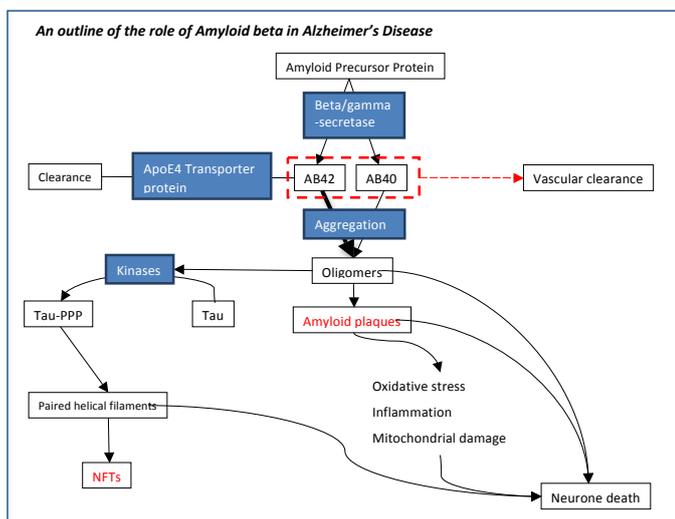
Research into the field of pathogenic seeding represents another possible way forward. Protein miss-folding occurs in neurodegenerative diseases such as AD, Parkinson’s Disease and ALS/Motor Neurone Disease.<sup>10</sup> As indicated above, it may be that miss-folded A $\beta$  oligomers act as seeds which induce more A $\beta$  miss-folding, and that this leads to a chain process similar to that seen in prion infections.<sup>11</sup>

Studies have already shown that small amounts of A $\beta$  injected into the brains of animals can initiate a chain reaction

9 *APOE* transports lipoproteins, fat soluble vitamins and cholesterol into the lymph system and then the blood. ApoE4 has also been shown to have a significant role in the development of atherosclerosis and in inflammatory processes.

10 There are multiple pathogenic proteins implicated in other neurological conditions. For example,  $\alpha$ -synuclein, huntingtin, superoxide dismutase-1, and TDP-43 are involved in conditions such as frontotemporal lobar degeneration, Parkinson/Lewy body disease, Huntington disease, and amyotrophic lateral sclerosis/MND.

11 Prion infections include Creutzfeldt-Jakob Disease and Kuru, a condition historically associated with ritualised cannibalism in Papua New Guinea. A prion is an abnormally formed protein that is capable of passing on its abnormalities to other proteins. There is also evidence that HSV1 viral infections increase AD risks.



of protein miss-folding that resembles the pathology of AD. Furthermore, there is evidence of A $\beta$  seeds in the brains of individuals who died from CJD as a result of receiving infected growth hormone factor (Jaunmuktane *et al.* 2015). More than 200 individuals developed CJD worldwide as a result of contaminated growth hormone therapy. An autopsy study of eight such patients found that four individuals, all under the age of 51 and with no pathogenic mutations linked to early onset AD, had severe grey matter and A $\beta$  pathology consistent with iatrogenic (treatment caused) transmission.

Work has now shown that A $\beta$  'seeds' have the ability to persist in the brain for months and regain their pathogenic properties when introduced to the right environment (Jucker & Walker, 2011). Whilst there is no evidence that AD is transmissible in the same way as prion diseases it may be that cellular or environmental seeds plus genetic factors could play a critical role in the initiation of AD.

## Will Significantly Better Treatments be Available by 2025?

At the 2013 World Dementia Summit it was agreed that 2025 should be set as a target date for the introduction of significantly improved therapies. Professor John Hardy says 'we are either very close, or very far away' from having more successful treatments. A great deal of interest is currently focused on ongoing clinical trials of the American research based pharmaceutical company Eli Lilly's drug Solanezumab,<sup>12</sup> a monoclonal antibody which binds to Amyloid beta plaques in the brain. There is preliminary evidence that the appropriate use of this medicine slows the development of early stage Alzheimer's Disease. Another example of ongoing industrial research is provided by a recently formed partnership between the Japanese company Eisai and the US biotechnology firm Biogen Idec. This is aimed at producing medicines which will reduce the production of Amyloid beta or help eliminate A $\beta$  oligomers after they form.

<sup>12</sup> Currently available evidence indicates that Solanezumab may be able to cut the rate of AD progression by around a third in its early stage cases.

More definitive data on the value of Solanezumab should become available in late 2016 or 2017. If it proves effective this may open the way to its being used as an early stage therapy, or as a protective agent in people at raised risk of developing symptomatic Alzheimer's Disease. This should also encourage further private and public investment into alternative products that may have more advantageous effects in given groups of people.

The view taken here is that the Solanezumab trials are, at least to a limited degree, likely to prove successful. But if this experimental treatment is found to be clinically ineffective a significant re-thinking of the possible ways forward will be needed. It may be that this would lead to more research in areas such as the role of vascular system pathologies in impairing amyloid beta clearance, and on 'prion theory' in the neurodegenerative disease context. Topics such as the role of brain cholesterol/lipid metabolism abnormalities in dementia could also receive increased attention.

## The Importance of Primary Prevention and Ongoing Biomedical Research

As with cancer, ageing is the main risk factor for dementia. People cannot stop growing older, and women – who are at a higher age standardised risk of developing dementias than men – cannot choose their birth gender. But in favourable social circumstances both males and females can seek to grow older as healthily as possible.

The presently available data suggest that about a third of AD/dementia cases may be preventable via the modification of key risk factors. 'Reducing your Risk of Dementia' was released by Alzheimer's Research UK and Public Health England (PHE) in July 2015. It has attracted considerable public interest, and highlights the fact that life style and allied choices proven to be protective against coronary heart disease, strokes, many cancers and type II diabetes also reduce individual and population level dementia risks. Public health priorities include stopping tobacco smoking, lowering blood pressure (and LDL cholesterol) levels, avoiding obesity in middle age (and other life stages), exercising regularly and moderating alcohol use.

The links between dementia and developmental and psychological factors need additional exploration, as do questions relating to whether or not lifestyle variations only impact on narrowly defined 'vascular' dementia or have wider roles. There is, for instance, currently some evidence that early life experiences during brain development and maturation, such as levels of nutrition and education plus high levels of cognitive activity later in life, affect dementia risks.

There are also reported correlations between experiencing depressive illness and the subsequent onset of dementia, although it is still unclear whether depressive episodes are on occasions manifestations of 'pre-dementia' states or should be regarded (perhaps because of the involvement of cytokines like IL-18) as independent risk factors. Likewise,

the interactions between Parkinson's Disease, strokes, traumatic brain injuries, type II diabetes, blood pressure levels and the various forms of dementia need further exploration.

Even a further 10 or 20 per cent reduction in age standardised dementia incidence rates could over time generate 100s of thousands of better quality life years and produce gross annual savings of in the order of £5 billion a year in the UK, including reductions in the private costs of avoidable disability and distress. However, lifestyle changes alone will not be enough to prevent most cases of dementia from occurring. There is therefore an ongoing need to invest in areas such as the genetics of the dementias and the roles of A $\beta$  and Tau protein in Alzheimer's Disease, whilst simultaneously emphasising the generic importance of primary prevention. Logically, the pursuit of disease avoidance and better means of therapeutic intervention are best seen as complementary as, distinct from rival, activities.

Despite the UK's positive record under the Cameron administrations, it is in this context of note that even today global governmental and charitable spending on dementia research is almost certainly no more than \$US 1 billion per annum (NIA, 2015). Even taking into account additional pharmaceutical industry outlays,<sup>13</sup> this figure remains low as compared with spending in areas such as oncology research, and very small against a Gross World Product of some \$80 trillion a year. Total dementia research spending from all sources is still unlikely to represent much more than 0.002 per cent of GWP, despite its combined financial and less tangible costs already being equivalent to approximately 1.5 per cent of GWP. Increasing spending on dementia related R&D should arguably be seen as a vital priority, albeit it ought not to be achieved at the cost of undermining other important areas of bio-pharmaceutical/ bio-medical advance.

### **Tertiary Prevention – Improving Long Term Care and Building Dementia Friendly Societies**

In an era in which both primary prevention and improved early stage treatment opportunities are rightly receiving increased attention, is also important to maintain awareness of the need to provide good quality care for those affected by advancing neurodegenerative disease. One way forward in this sphere involves building strengthened public and professional awareness of the capabilities as well as the disabilities of people living with dementia, partly in order to

reduce undue restrictions on their freedoms while still paying appropriate regard for safety and protective care needs. If, for instance, more people in a community understand the symptoms of dementia they will be better placed to provide appropriate help for individuals who have become lost or confused. This is a form of tertiary prevention.

With regard to improving pharmaceutical care and pharmacy based services, possible interventions range from making further attempts to prevent the improper institutional use of anti-psychotic medicines to sedate people with dementia for 'patient control' as distinct from personal care reasons (past denials of the value of medicines known as acetylcholinesterase inhibitors or AChEIs while they were relatively expensive may on occasions have encouraged inappropriate low cost alternative approaches to care) through to improving home support. Starting to have problems with medicines taking can be an important early sign that individuals are in need of additional care, albeit that such phenomena can sometimes wrongly be seen as examples of '*patients being wasteful*' as opposed to being valuable indicators of increasing care requirements.

In future community pharmacists may, in addition to winning extended roles in early stage dementia detection and personal care, also play more useful parts in the delivery of preventive care via enabling more people to adopt healthy life styles and use medicines to best effect in contexts such as vascular disease prevention. Improving the population wide control of blood pressure levels is one area where this should already be possible, were policy makers and the public more adequately informed and supported. Pharmacists working in independent community settings might in addition enhance public access to genetic testing and other forms of risk assessment and early disease testing. This could in time prove highly cost-effective for the NHS, as well as of personal value to individuals seeking to protect their own health and that of their families as efficiently as possible – see '*Primary Care in the Twenty First Century*'.

However, in the immediate future the most important priority in Britain (and particularly in England) is arguably to improve equitably funded access to good quality residential and well-coordinated health and social care for people living with the later stages of Alzheimer's Disease and other disabling forms of dementia. From the inception of the NHS Local Authority provided social care has been means tested, while NHS care has been free. Over time this divide has been linked to the closures of NHS facilities for people with long term care needs in both the community and in institutional contexts. In some ways this has been desirable. But on occasions 'social care' has been expanded to take on roles that it has not been best equipped to play, while the number of skilled nurses employed in the community and in some types of residential care has declined.

The problems this has caused are currently being exacerbated by reductions in the funding available for social care. Although measures are now being taken to address the latter challenge, the next few years are likely to see increasing difficulties for many individuals and families

<sup>13</sup> The available literature indicates that there have been over 200 failed pharmaceutical industry attempts to have developed new AD/dementia medicines in the last 10-20 years. One of the most important of these was the work undertaken by J&J and Pfizer on Bapineuzumab, which involved costs of over \$1 billion. This poor success record coupled with concerns as to the length of intellectual property protection available for medicines that may not prove their full worth until one or two decades after they are first marketed is currently discouraging investment. However, some sources suggest that there are still over 50 potential treatments for dementia in industrial development – see Marsden and Mestre-Ferrandiz, 2015.

affected by dementia. Yet view taken here is that at the national level achieving improved standards of care is far from unaffordable, should sufficient electoral and political will exist. Although according to agencies such as the WHO (2015) the UK's record in this area is already relatively good compared with that of many other nations, it is lagging behind that of world-leaders such as the Netherlands and Sweden.

In this sense at least the original promise of the NHS is not being kept because of failures to modernise the overall welfare system in contexts like that of dementia, and to protect professional care standards as well as the (equitable) financial viability of the 'welfare State' and all the families and individuals using its services. If and when the public becomes better informed about this situation and the actions that could remedy it, pressures for reforms that will not only provide universal protection from 'catastrophic' care costs but also help ensure good quality support for everyone unfortunate to develop conditions such as Alzheimer's Disease are likely to grow significantly.

## Conclusion

There are many questions relating to the future prevention and treatment of Alzheimer's Disease and other dementias that have not been explored in this *Media Briefing*. For example, in the context of medicines development they include 'are current intellectual property provisions sufficient to attract adequate levels of private risk capital into areas in which it may take twenty or more years of post-marketing use to demonstrate the full value of an innovative medicine?' and 'will treatments that offer limited but nevertheless incrementally significant outcome improvements in dementia care be judged cost-effective by HTA assessments as they are currently undertaken by bodies such as NICE and its equivalents elsewhere in Europe?'

It remains to be seen whether or not twenty first century Britain will prove as good at maintaining and developing world-leading industries and a commercial environment that appropriately fosters life-science based innovation as it is in promoting excellence in non-commercial arenas. However, the most important point to end with here is that advances in the biological and allied sciences will without doubt eventually make better preventive and ameliorative treatments for neurodegenerative diseases possible. Investing in well organised research will ultimately bring rewards for both individuals and communities that far outweigh their costs, even if obtaining future gains on occasions requires current sacrifices.

Achieving this end will demand advances based on economic and social science insights, as well as excellence in the physical sciences. But provided that access to good quality health and when needed social care can be maintained and where necessary improved, there is robust reason to believe that by or before the 2050s the burden of distress caused by conditions such as Alzheimer's Disease will – if not totally eliminated – be dramatically reduced.

This will allow ageing individuals and societies alike to live on in not only material prosperity, but with increased psychological well-being and greater justice.

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