

“A STITCH IN TIME SAVES NINE” – INVESTING
MILLIONS IN ALZHEIMER’S RESEARCH NOW WILL
SAVE BILLIONS LATER

BY

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PASS WITH DISTINCTION

RESEARCH PAPER
BASED ON
PATHOLOGY LECTURES
AT MEDLINK 2009 or MEDISIX 2010

Abstract

Estimates of the cost and prevalence of Alzheimer’s disease have been revised upwards and all three main political parties in the UK are committed to increased research funding. Public awareness is growing. This paper reviews the most recent research and indicates how developments in areas such as treatment with stem cells might eventually offer the possibility of cure rather than delay in disease progression. Ethical dilemmas are discussed at the end of the paper.

INTRODUCTION

Prevalence and Funding.

Alzheimer’s disease (AD) is the commonest form of dementia – a progressive clinical syndrome characterised by memory loss, disturbances in language, psychological and psychiatric changes and impairments in activities in daily living. Dementia directly affects 820,000¹ people in the UK (Fig 1). Each individual with dementia costs our economy more than £27,000 pa - a total cost of £23bn a year. The social impact on carers families and friends is incalculable. Age is the most significant risk factor with nearly 5% of 65y olds having AD and the prevalence doubling with every 10 years of age Success in

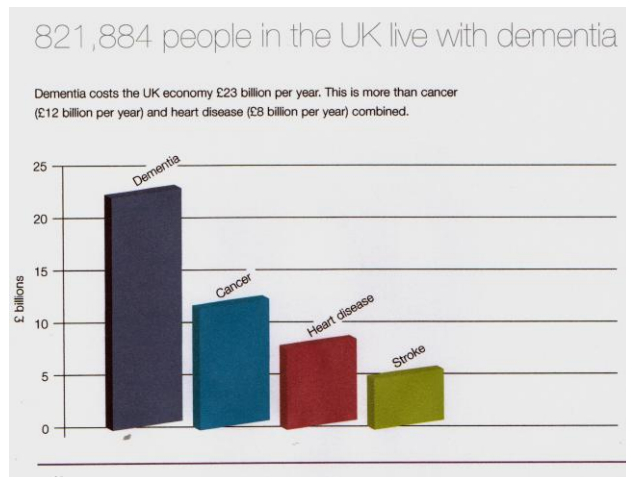


Figure 1

elongating human life span means that over the next 30 years, in the absence of any dramatic breakthrough in treatment, the number of people with AD is likely to double and the cost triple. Compared to the high economic burden of dementia, patients with cancer cost £5,999 pa and those with heart disease £3,455 pa, yet the spending on cancer research is 12 times higher than on dementia research This discrepancy in research funding is clearly

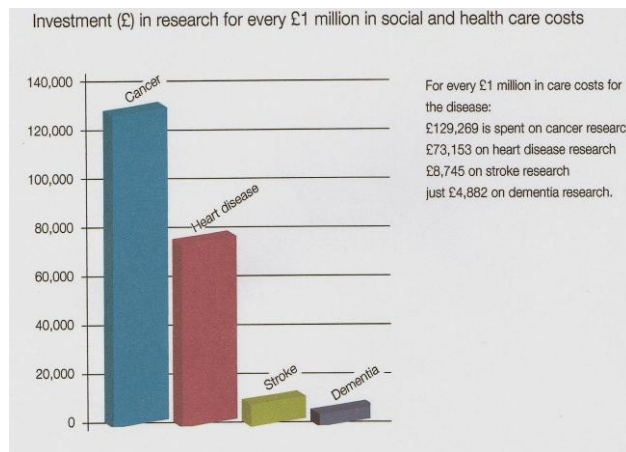


Figure 2

shown when the relative expenditure on research for every £1million in social and healthcare costs is considered (Fig 2) .

National Dementia Strategy in England

The National Dementia Strategy² was launched in February 2009 with the objectives of raising public awareness, diagnosing the disease early on and improving quality of care. A Ministerial Dementia Research Summit³ was held in July 2009 to help identify priority areas for research and how barriers to AD research can be reduced.

Pathophysiology

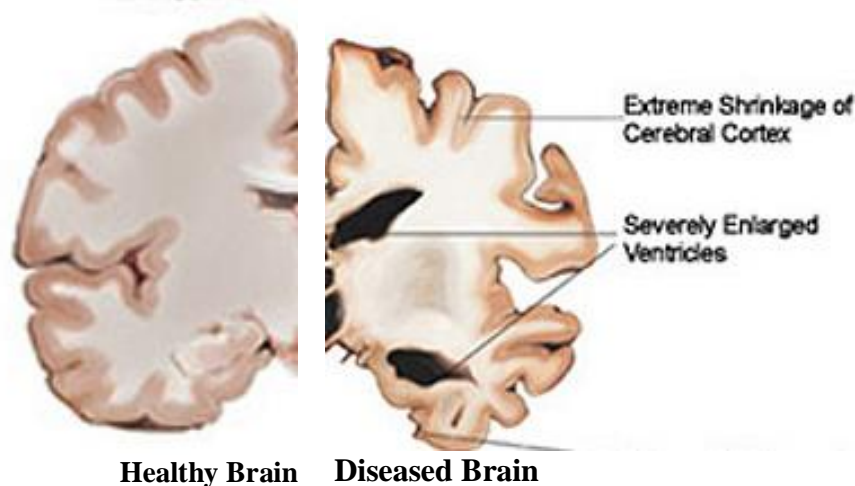


Figure 3

When an autopsy was performed on Dr Alois Alzheimer's patient, Auguste D, in 1906 samples of her brain were stained and the amyloid plaques and neurofibrillary tangles (Fig 4) that are so characteristic of the disease were seen for the first time.⁴ The ventricles which contain cerebro-spinal fluid, were enlarged and the cerebral cortices, temporal lobes and hippocampi had all shrunk (Fig 3) due to loss of neurones. This typical degeneration can continue until the brain is a fraction of its normal size. We now know that the amyloid plaques are not formed from starch but from small peptide fragments of amyloid precursor protein (APP), a transneuronal protein, which clump together as dense insoluble deposits of amyloid-beta ($A\beta$) proteins. The neurofibrillary tangles develop when microtubule tau proteins become hyperphosphorylated and aggregate within the neuronal cells.

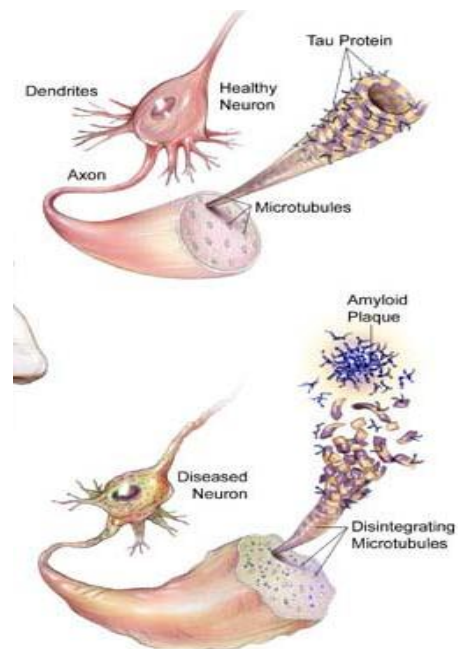


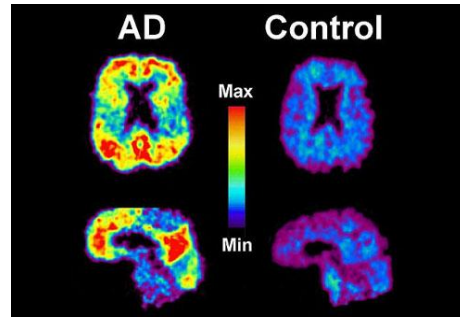
Figure 4

Neuronal and particularly synaptic loss is the main cause of cognitive and behavioural symptoms in AD. Clearance of plaques by targeting $A\beta$ has been the main focus of possible treatment but there is now an increasing emphasis on the associated inflammatory response. A recent paper⁵ has shown an increase in the density of microglia, the main representative of the immune system in the central nervous system, before both plaque formation and the activation of the microglia by extracellular $A\beta$ accumulation.

Neuro-imaging

Imaging techniques provide an excellent means of examining the living brain and allow detailed volumetric measurements of the different structures. The latest generation of MRI (magnetic resonance imaging) scanners enable detailed 3-D visualisation, especially of the hippocampus. PET (Positron emission tomography) is

being used increasingly to assess the progression of AD with radioactive tracers to target different areas of the brain with specific molecules. Typically fluorodeoxyglucose (FDG) is used. This is taken up by active mitochondria so that the metabolic activity of the brain can be measured. A recent development⁶ with great potential is the use of Pittsburgh compound B

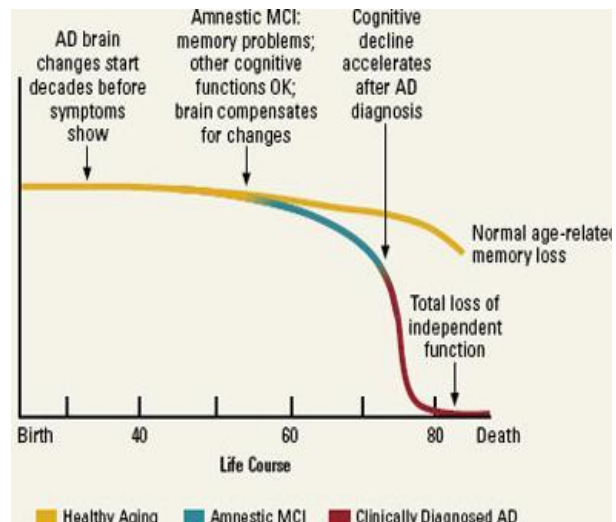


(PiB) which binds to A β protein. In this way PiB scanning (Fig 5) can be used to show how changes in the brain, such as amyloid plaques, develop well before symptoms appear.

Fig 5

Early diagnosis

Giving people with dementia an early and accurate diagnosis is a key aim of the National Alzheimer Strategy. Individuals and carers can then be given good quality information and guidance. It has been decided, though, that at this stage earlier diagnosis should be achieved by increasing public awareness rather than by screening. The graph demonstrates how changes in the brain appear many years before AD is diagnosed. One study⁷ revealed that when symptoms first appeared nearly one quarter of all caregivers waited more than a year before making their first appointment with the doctor. Further delays can occur because GPs may be reluctant to label patients as suffering from dementia when there is no “cure”. The diagnosis of AD requires investigations, such as MRI and CT scans that are only available to specialists. Earlier detection would enable research on treatment strategies before the disease process becomes too advanced. Effective tools to screen for AD and make earlier diagnoses are now available.



The mini-mental state examination (MMSE) has been the standard short cognitive test for 30 years but new powerful valid screening tests are now being developed. A cross sectional study on the self administered “Test Your Memory” (TYM) test⁸ was published last year. It is more sensitive to mild Alzheimers than the MMSE, tests a wider range of cognitive domains and requires minimal operator time.

The potential of imaging techniques to make early diagnoses has already been mentioned. Although PiB scans are currently used as a research technique further developments and the falling costs of technology could see this being used as a standard diagnostic test in the future.

CSF measurements of tau and A β (especially a component known as A β 42) can now be used reliably as biomarkers⁹ and are beginning to be used for multicentre drug trials in the earliest pre-symptomatic stage of AD. Standard protocols are essential to avoid site-to-site and batch-to-batch variation. With further research new generations

of CSF and blood biomarkers are likely to be developed and it may be that these will be used diagnostically.

Nerve cell death is the key event of all neurodegenerative diseases. Until recently it has not been possible to study this in real-time. A paper published in November 2009¹⁰ caught the public imagination when it suggested that retinal screening might become a reliable non-invasive test for AD. The study involved the use of fluorescent cell death markers in an “animal model” of transgenic mice programmed to develop AD. Single cell death profiles were tracked in the retina of the living eye as AD developed “over hours, days, weeks and months”. Much more research needs to be done but the technique could eventually be used both for researching the effects of potential new drugs on the human brain and for early diagnosis.

Prevention of AD

Case-control studies have linked several risk factors with AD¹¹. These include age (which has already been discussed), family history, genetic risk factors (see below), head injury, depression, blood pressure, diabetes, high cholesterol, atrial fibrillation (irregular heart beat), the presence of cerebral emboli and low physical and cognitive activity. In the last year there has been increasing evidence that diet, coffee in women, specific anti-hypertensive (BP) medication and even mobile phone use be protective. Stress, when associated with disturbance of circadian rhythm also appears to be a risk factor.

Evidence that diet could prevent AD may be strengthened by a study due to be presented to the American Academy of Neurology¹² in April this year. The study has found that people who closely followed a “Mediterranean diet”, rich in vegetables, fruit, fish red wine and monounsaturated fatty acids such as olive oil 36% less likely to have brain infarcts (dead areas of brain tissue caused by small thrombi and emboli) than those who did not follow the diet. At this stage it is not clear how well matched participants were for confounding variables such as age, BMI, BP and cholesterol levels.

An increasing trend may turn out to be the patenting of naturally derived compounds that appear to have a protect effect on the brain. One example is NIC5-15, a compound derived from pine bark and foodstuffs such as soy and carob. It is currently being evaluated in mid-stage clinical trials at the Mount Sinai School of Medicine¹³.

A French study¹⁴ involving 7,000 people has shown that women over 65 who drink over three cups of coffee a day are less likely to show cognitive decline.

Gingko Biloba is a herbal supplement that is widely taken in the hope of improving, preventing or delaying cognitive decline however a large randomised double-blind, placebo controlled study¹⁵ published towards the end of 2009 has shown no evidence that gingko is effective.

The protective effect of statin drugs, that lower cholesterol and have anti-inflammatory effects, has been shown in several studies though two recent studies¹⁶ have now cast doubt on this. A study last year¹⁷ showed that some types of anti-hypertensive (BP) medication, such as angiotensin receptor blockers (ARBs), have a greater ability to prevent AD than others. This effect is not directly related to their effect on blood pressure.

A number of studies have demonstrated the protective effect of exercise. A robust study¹⁸ in 2006 suggested that the risk of developing dementia was 38% lower in adults who exercised for at least 15 minutes three times a week.

Stress is a less well recognised preventable risk factor. 3-dimensional volumetric scanning has demonstrated an association between stress in humans from loss of circadian rhythm and recognition memory loss, an early sign of AD, due to atrophy of the perirhinal cortex¹⁹. More research needs to be done urgently as the implications for lifestyle and certain occupations are enormous.

An intriguing study²⁰ published in January 2010 found that the memory impairment of transgenic Alzheimer mice disappeared when they were exposed to “high frequency” electro-magnetic radiation over several months. This raised the possibility that mobile phone use might actually protect the brain from AD.

Genetic risk factors

Until last year the only known genetic risk factor for late AD was apolipoprotein (ApoE) located on chromosome 19²¹. Its three gene forms are e2, e3 and e4. The higher the number the greater is the risk of AD. 40-80% of the AD population are either homozygous or heterozygous for the e4 allele compared with 10% of the general population.

Now by comparing half a million variations in the genetic codes of 4,000 people with Alzheimer’s disease and 8,000 healthy people British researchers²² have identified two more common genetic variants that act as risk factors for AD. One is located near the Clusterin (CLU) gene on chromosome 8 and the other is associated with the PICALM gene on chromosome 11. A French team doing similar genome-wide association studies have identified a third variant near the Complement receptor 1 (CR1) gene. One in five of the population carry at least one of these three genes.

Faulty ApoE causes a build-up of A β and until recently this was considered to be the key event in the development of AD. Treatment strategies to remove the amyloid plaque have therefore been a key focus of research for many years. The discovery of these three gene variants supports the hypothesis that inflammation and a faulty immune response might be the primary event. Normally Clusterin and the CR1 gene dampen down and control aspects of the immune response, including an immunological chain reaction, called the complement cascade, which rids the body of unwanted cells, toxins and proteins. The normal version of CR1 also helps prune synapses, the neuronal connection, destroyed in AD. In people with the mutated form of CR1 it could be that this process goes into overdrive and destroys too many connections. The PICALM gene draws fats and proteins into cells and may be active around synapses. With age blood vessels become damaged and an 8 year longitudinal study using serial PET scans to measure cerebral blood flow has confirmed this occurs more rapidly in ApoE4 carriers. All three gene variants could affect a person’s ability to repair the cerebral circulation. Removing the detrimental effects of these genes through specific treatments based on greater understanding of the pathways they control could reduce the proportion of people developing Alzheimer’s by as much as 20 per cent.

Unlike the above genes which increase the risk of AD a gene variant that protects against age-related illnesses, was identified in 2003. Cholesteryl ester transfer Protein (CETP) gene is known as the longevity gene²³. About 8 per cent of people aged 70 have the CETP variant but this rises to 25 per cent among centenarians. A recent study has shown that people who carry the gene have their risk of AD reduced by 70%. This study therefore confirms the importance of genes that regulate cholesterol metabolism.

Current management of AD

Guidelines for the support of people with dementia and their carers were published by the National Institute for Clinical Excellence (NICE)²⁴ in November 2006. The guidelines advised on pharmacological and non-pharmacological management of AD as well as the complex out-of-character behavioural and psychiatric symptoms associated with AD. Most of this advice was broadly welcomed especially advice to consider carefully the use of anti-psychotic medication which may increase the risk of stroke and adversely affect cognition. However NICE also carried out a controversial cost effectiveness analysis²⁵ on cholinesterase inhibitors. These drugs have been shown to modify symptoms by inhibiting cholinesterase the enzyme which breaks down acetylcholine - an essential neurotransmitter. To the distress of many sufferers and carers and the disapproval of some psycho-geriatricians the agency has recommended that cholinesterase inhibitors should be restricted to patients suffering from moderate disease.

Other recent research trends

I. The drug “pipeline”

As of June 2008 there were 682 drugs in development of which only ten were in phase 3 trials²⁶. Generally the time for phase 3 to clinic is about five years.

The table opposite shows a few of the drugs that are being actively researched or whose trials have recently been completed or discontinued. Results have generally been disappointing with drugs at best managing only symptoms. Many potential new treatments have targeted A β but the amyloid vaccine studies have recently failed as has the phase 3 trial of Dimebon²⁷, a hayfever treatment that had a successful phase 2 trial in Russia. γ Secretase is involved in the formation of A β and trials of γ Secretase inhibitors have also been disappointing. Many compounds fail because of toxicity. This partly explains the high number of trials with existing drugs. Efficacy is difficult to demonstrate because of a lack of biomarkers and inadequate standardisation of those that exist. Transgenic mice have been developed to produce plaques but there are no animal models that show the tangles produced in humans.

Anti- inflammatory	Ibuprofen, rofecoxib
Prevent phosphorylation	
Antioxidants	Vit E
Immunotherapy	anti-amyloid antibodies (γ globulin) human immune mma globulin MABT5102A (monoclonal a'body)
Neuronal nicotinic agonist	Ispronicline, varenicline
Plaque clearance	Bapineuzumab
Reduce/prevent plaque formation	Secretase inhibitors: EHT 0202,
Inhibition of cholinesterase	Donepezil, rivastigmine
Oestrogen	Premarin
Genetic growth factors	Nerve growth factor (NGF)
Other	Statins (cholesterol lowering agents)

With imaging techniques and biomarkers demonstrating pre symptomatic disease in people who are cognitively “nomal” there is now much interest in the development of drug trials in this prodromal period. The Alzheimers Prevention Initiative (API)²⁸ aims to recruit people with genetic risk factors and abnormal scans.

Awareness that many elderly people have plaques and tangles but do not have Alzheimers is stimulating interest in alternative research not directly connected with A β . cAMP response element binding protein (CREB)²⁹ is a key player in the formation of new memories. Blocking the phosphodiesterase enzymes, which

degrade cAMP, can boost levels and enhance cognitive performance in mice, tested with routine tests such as the mouse water maze. CREB appears to act by stimulating dendritic spine formation and its effect is independent of plaque load.

A placebo controlled trial has just been announced into the safety and tolerability of Etanercept (Embril)³⁰ with effects on cognitive, behavioural, functional and immunological outcomes being examined as secondary. Controversial claims³¹ have been made that for this anti-inflammatory drug that has been widely used in the treatment of rheumatoid arthritis for several years. At least 50 patients with AD have been treated at the Institute for Neurological Research, a private clinic in California. Patients are injected into the back of the neck and it is claimed by Professor Tobin that several have shown an improvement in verbal and other cognitive skills within minutes. Although families have posted their videos on YouTube the response of most experts has been sceptical. Research has shown that levels of a “cytokine” signalling factor called Tumour necrosis factor (TNF)-alpha can be up to twentyfive times higher in the CSF (cerebro-spinal fluid) of AD sufferers. This attracts immune cells but Etanercept binds to it and makes it inactive. The trial result will be awaited with interest by many people.

One criticism of Embril therapy has been that it is not clear whether it crosses the blood-brain barrier (BBB). This is a problem for many potential treatments with large or lipid insoluble molecules. Nano-medicine³² is a rapidly growing area of research which offers the possibility of using lipid or polymer based nanoparticles to cross the BBB and increase bioavailability.

II. Stem cell research

Regenerative medicine using stem cells is developing rapidly and although there are many problems to be solved it is increasingly showing the potential to provide cures for neurodegenerative conditions such as AD. Stem cells derived from embryonic tissue (ESCs) are totipotential meaning they have the ability to differentiate into any of the many different types of specialised cell in the body. Neural stem cells (NSCs) are found in the brain are pluripotential having the ability to develop into neural tissue such as neurones and the active supportive “glial” tissue. Some differentiated cells such as fibroblasts³³ can be made to turn back into stem cells. These are known as induced pluripotential stem cells (iPS cells). In January this year³⁴ it was reported that researchers had found a way of turning fibroblasts directly into induced neuronal (iN) cells. The disadvantage of ESCs is that they may be rejected as the immune system recognises them as foreign. They also have a tendency to form tumours called teratomas consisting of several tissue types. iPS and iN cells derived from the patient would be a perfect match. They can now be produced without harmful “transgene” sequences.

The brain is continually producing new neurones. French scientists have recently shown that neurons born in the hippocampus throughout adult life strengthen and update spatial memories.³⁵ Newborn neurones incorporate themselves into circuits when new memories form. Young neurones grow spines that in time become richly branched dendrites. To begin with a dense network of connections is established followed by a pruning of some synapses and branches leaving others that are regularly used to become stronger. Remodelling is known as synaptic plasticity. The small percentage of dendrites that persist may be responsible for long term memories³⁶. MicroRNA is involved in the differentiation of stem cells and formation of new neurones and acts by switching genes on and off. One of the genes involved in

memory formation is called c-fos. Several mRNAs have been identified in dendrites and synapses. We are just beginning to understand something of the complexity involved in the production of new neuronal networks. Research into micro-RNAs³⁷ will be essential.

Recent research³⁸ involved injecting the hippocampus of transgenic mice programmed to develop AD with NSCs. They migrated to an area of the hippocampus known as the dentate gyrus where they differentiated into various neural cells. Synaptic density doubled but there was no alteration in the amyloid plaque. Memory measured by standard techniques increased substantially. A neurotrophic factor called Brain Derived Neurotrophic Factor (BDNF) was shown to be secreted by the stem cells and neighbouring cells. Further interesting work is being done on BDNF³⁹.

Ethical Issues –a few of many

The individual

Failure to value people, however forgetful they may be, risks making them more vulnerable to harm.

The National Alzheimer Strategy encourages early diagnosis but not screening for AD. Is it always beneficial to diagnose AD when there is no effective treatment? A diagnosis might increase suffering through anxiety or depression.

When should an individual give up control over finances and important decisions? A relative may be appointed to have Power of Attorney and act in their best interest, but there may be issues over when power should be transferred.

The balance between an individual's freedom and the need to protect them and others can be difficult. For example cooking with gas or driving.

Professionals and carers should make sure that AD sufferers are treated for pain and other medical conditions such as depression. Medication to control behaviour, such as anti-psychotic drugs, should only be used occasionally as it can cause strokes and make confusion worse.

Funding

Only people with moderate AD receive anticholinesterase drugs although there is evidence that they may be effective in treating some people with mild and advanced disease. Cholinesterase inhibitors cost £70M a year. This could fund elderly care doctors or be put towards developing 'hospice' style units where palliative care expertise could be developed.

The case for a large boost in research funding is overwhelming and needs to be acted on now. The proportion allocated to cure future generations must be balanced against optimising care for sufferers today.

Research

Use of embryonic stem cells in the UK is controlled by the Human Fertilisation and Embryology Act (1990) and the Human Fertilisation and Embryology (Research Purposes) Regulations 2001. Moral objections from individuals and religious groups persist.

ESCs begin to differentiate at the eight cell blastocyst stage. They are harvested from spare embryos that are not going to survive and the cell lines produced will prevent suffering in hundreds of thousands of individuals in future generations. With greater discussion more people might see a moral case in favour of stem cell research.

Conclusion with suggestions for other future developments

The pharmacological approach based on the amyloid cascade has so far been disappointing though collaborative research on prodromal AD in individuals with genetic risk factors may prove more fruitful.\

Stem cell research has rapidly shown great potential for curing AD.

Our understanding of the role of neurotrophic factors, such as BDNF, and of the mRNAs is in its infancy. My reading suggests that rather than stem cell transplantation it is likely to be the knowledge we gain from understanding how neurogenesis is enhanced and controlled that will lead to real breakthroughs.

Studies need to be done in higher primates to see whether the successful research done on rodents is transferable.

Research in these animals must also be done on ways of delivering stem cells across the blood-brain barrier.

I would like to see studies done on whether it might be possible to deliver NSCs, mRNA or neurotrophic factors to the hippocampus and cerebral cortex via the ventricles by intrathecal injections (like epidural lumbar punctures used to control the pain of childbirth) or by injecting the small vein network high in the neck. This is a technique used by Professor Tobin when giving patients his “miraculous” Embrel treatment! NSCs seem to have the ability to migrate to areas where they are needed and it is only a short distance from the ventricles to the hippocampus.

Another ‘delivery’ solution might come through the development of nanotechnology. It might be possible to combine nanoparticles with monoclonal antibodies which could then target and deliver neurotrophic factors such as BDNF to specific areas of the brain such as the hippocampus or neocortex

Given the human tragedy and serious economic consequences of failing to find a cure, there should now be massive investment in research. Regenerative medicine, in particular, now shows the potential for real cure.

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