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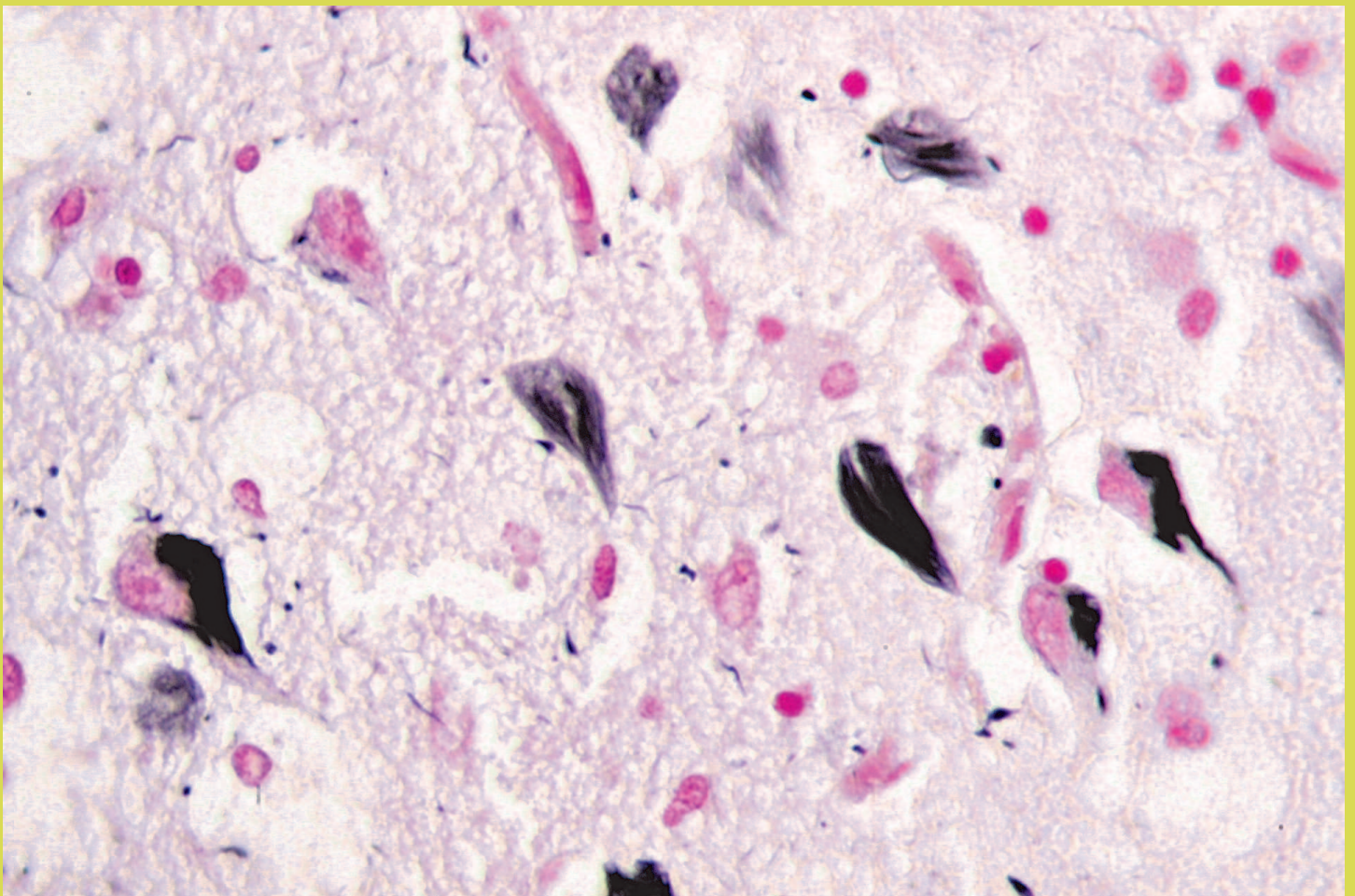
**Alzheimer's
Society** | Leading the
fight against
dementia

Research newsletter

Quality Research in Dementia

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Issue 123

Recently completed research | When, where and how does Alzheimer's disease start?



Goodbye, from Steve Dewar, Interim Director of Research and Development



At the end of the year I am leaving my role as the Society's Interim Director and handing over to Dr Doug Brown. The team and the Society will benefit from a new full-time director at a time of growth and ambition.

It has been a great year of learning for me and I will reflect on my work with the Society with pride. The passion and commitment of the team, the organisation and the voluntary support is an inspiration that has given work meaning and relevance. During my time in the interim role I have learnt much and foremost in my mind is the urgency and importance of dementia research.

Behind the projected rise in the numbers of people living with dementia (1 million by 2021) are the realities of an ageing society. By 2035, 23 per cent of the population will be over 65 and 3.5 million of us will be over 85, yet older people will be more often living alone with limited support from friends and relatives, in

communities where more of us work and less of us are able to provide care. All this in a world where constraints on resources and the numbers of health and social care professionals is likely to mean that there is less professional help available.

My belief is that research is vital to enabling us to face this challenge, enabling better care as well as continually seeking the breakthroughs in cause, prevention and cure that will come with greater understanding. The combination of sound research and the trusted voice of the Society can be powerful in creating an understanding of this challenge and ways in which we can all respond.

Good research can capture public attention. It can spread understanding of the disease and the needs of people living with dementia. It can spur people and organisations to action and has the power to help us understand how to organise and support people to give the care that will be needed. It can also ensure that Alzheimer's Society is effective in what it does and help us attract the support it needs to extend reach and impact.

With such a vital role ahead it is pleasing to see the Society recognise the importance of research: increasing investment, attracting new funding partners, extending research ambitions and

growing the team. I will watch with huge interest and have nothing but the utmost trust and respect for those who will lead our contribution.

Finally, I wanted to thank the Network, the team and the organisation for the consistent welcome, support and commitment which has characterised each day in the job — it has been much appreciated and it is a fabulously positive experience for me to take into my next challenge. Thank you.

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On the cover

Tau tangles, a hallmark of Alzheimer's disease, in the hippocampus, an area commonly affected by the disease. Find out more about the findings from a research project investigating tau on page 4. (Image by Patho).

Research in the press



An overview of research stories that have made the national press in the last month and how Alzheimer's Society commented on them.

Last month, Alzheimer's Society and the government announced a new initiative to train 1 million 'Dementia Friends' by 2015. Dementia Friends, supported and funded by the government, aims to increase dementia awareness and change the way the nation thinks, talks and acts. The drive forms part of the six-month progress report on the Prime Minister's challenge on dementia.

Jeremy Hughes, Alzheimer's Society's Chief Executive, welcomed the scheme saying, 'Nearly two-thirds of people with dementia tell us they feel lonely and almost half report losing friends. With one in three people over 65 developing dementia it is vital we change this picture.'

'Dementia Friends is not about 1 million token gestures. It's about rallying 1 million people from all corners of England to help make a better life for people with dementia. This is a huge ambition, but we are confident we can not only meet it but beat it. Dementia

is everyone's problem and we all need to be part of the solution.'

You can find out more about the Dementia Friends programme and register your interest at dementiafriends.org.uk

A study by researchers at the NIHR Biomedical Research Centre at St Thomas' and St Guy's NHS Foundation Trust, and King's College London, has produced more evidence that cardiovascular risk factors increase the risk of developing dementia. The study looked at more than 8,000 adults, and found that those over the age of 50 who smoked, had high blood pressure or were at increased risk of a stroke, performed less well on a range of tasks designed to test memory recall, verbal fluency, attention and other cognitive skills.

Jess Smith, Research Communications Officer, said, 'We all know that smoking, high blood pressure, high cholesterol levels and a high body mass index are bad for our heart. This research adds to the huge amount of evidence that also suggests they can be bad for our head too.'

'One in three people over 65 will develop dementia but there are things people can do to reduce their risk. Eating a balanced diet, maintaining a healthy weight, exercising regularly, getting your blood pressure and cholesterol checked and not smoking can all make a difference.'

The Prime Minister announced additional funding grants from the government's Biomedical Catalyst fund, for technology to cut the amount of time it takes to receive a dementia diagnosis. The £29.6 million fund will be managed by the Technology Strategy Board and includes a grant that will combine brain imaging technology with computerised cognitive testing.

Jeremy Hughes commented, 'Many people with dementia face a wait of months or even years for a diagnosis and fewer than half ever receive one. This means hundreds of thousands of people are living in a state of limbo without access to treatment and support to live well. This government funding has the potential to reduce the wait for a diagnosis, give GPs the confidence to diagnose and reflects a commitment from the government to tackling dementia.'

'With 800,000 people in Britain living with the condition, dementia is the biggest public health challenge facing Britain today. As numbers double and costs soar, developing earlier ways of diagnosing the condition and ensuring we support people after they are diagnosed to live a full and independent life as long as possible are vital.'

Research update: Recently completed research and a research publication

Completed research: How does hyper-phosphorylated tau cause nerve cell degeneration?

Dr Amritpal Mudher, University of Southampton

Dr Amritpal Mudher was previously an Alzheimer's Society Research Fellow, and now leads her own laboratory at the University of Southampton. This project grant, awarded in 2009, is one of our key research grants investigating the role of tau in Alzheimer's disease. Dr Mudher also currently holds another project grant from Alzheimer's Society, further investigating how tau causes neurons to die.

Using a fruit fly model of Alzheimer's disease we have shown that in the presence of the abnormal human tau protein the 'tracks' inside nerve cells, over which material is usually transported, break down. One of the aims of this grant was to shed light on the mechanism by which these tracks break down.

We have shown that the abnormal human tau is not able to attach to the tracks as it should and this is one of the reasons why they collapse in its presence. One of the aims of our research has been to work out whether agents that can 'Sellotape' the collapsed tracks together may be used to prevent the disruption of transport inside these nerves. We have found that agents such as Paclitaxel and NAP10, which are known to bind to and stick together microtubules (tubes within a cell, including tau, that make up its skeleton), are able to improve the behaviour of fruit fly larvae that are expressing (producing) the abnormal human tau.

We studied the nerves of the tau flies with a high resolution

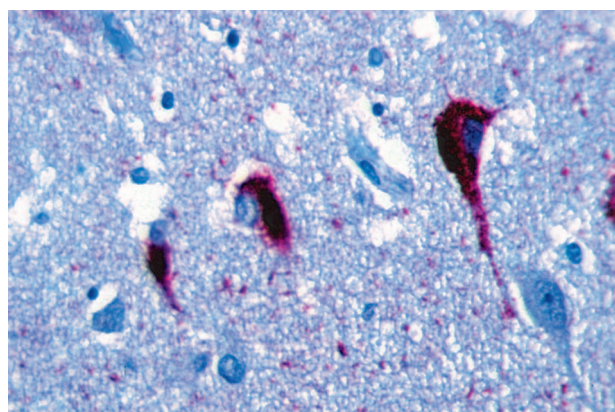
microscope called the electron microscope and found that there are many more intact tracks in NAP10 treated tau flies than in untreated flies. We then went on to show that transport of materials over the more intact tracks in the treated tau flies is dramatically improved and looks very similar to what it is in normal flies. Our results imply that treatment with the drug that can stick tracks together has the ability to reverse all the detrimental effects of abnormal tau: reinstating the broken tracks, improving the transport of materials over them and then leading to improvements in behaviour of the animals. We have presented our results at national and international conferences in the last year and

hope to publish these findings in the important journal *Molecular Psychiatry*.

Additionally, we have continued to investigate whether increasing the amount of 'anti-stress' proteins such as 'chaperones' (which belong to a class of proteins that normally get produced in cells in stressful situations) may protect the nerve cells from the damaging effects of the abnormal human tau.

We have generated flies that express both human tau and a chaperone protein and we find that these flies are much more resilient to the toxic effects of human tau than flies expressing the human tau alone. The experiments we have conducted

Tau tangles are a hallmark of Alzheimer's disease. Dr Mudher and her research team have been using a fruit fly model to better understand how tau causes neurons to die, and to find some substances that might help to prevent this. (Image by Patho).



so far have used oxygen deprivation as a means of stressing the flies and we find that many of the tau expressing flies die soon after this stress and those that survive are not able to fly or climb about easily. However, the flies that express both the human tau and chaperone are remarkably different to the tau

flies without the chaperone – none of chaperone/tau flies died after this stress and most of them regained their climbing and flying abilities. These results are preliminary but clearly suggest that one way of overcoming the toxic effects of human tau may be to increase the amount of anti-stress responses in the cell – like

increasing the amount of chaperone proteins. We had begun to repeat these preliminary studies but due to time constraints were unable to complete them. Perhaps this will be the subject of a future grant.

Research publication: Clusterin is crucial in making amyloid-beta toxic in Alzheimer's disease: Understanding the pathways involved

Dr Richard Killick, King's College London

Dr Richard Killick and his research team at King's College London have recently published a paper based on the work of investigating the way that amyloid-beta is toxic in Alzheimer's disease.

Amyloid plaques lead to the formation of tangles of tau protein, found inside the brain cells. This causes the death of brain cells, which brings about the symptoms of dementia. Although it has been accepted for over 20 years that the progression of dementia is driven by amyloid and results in abnormal changes in tau, the exact mechanisms of the disease remain something of a mystery.

Recent genetic studies have identified the gene for a protein called clusterin as a risk factor for late-onset Alzheimer's disease. Levels of clusterin are also known to be elevated in the blood of people with Alzheimer's from an early stage in the disease, so the researchers wanted to find out what role it might play in the progression of disease.

The project looked first in mouse brain cells grown in the laboratory and found that the presence of amyloid alters the amount of clusterin in these cells. Clusterin then acts to switch on a pathway of molecular signals that drives the changes in tau that are associated with the formation of

tangles inside the cells, another hallmark of the disease.

When this signalling pathway was kept switched on in a mouse model of the disease, the researchers observed an increase in tangle formation and evidence of cognitive defects.

These findings are incredibly important; understanding more about the way in which amyloid causes brain cells to die will provide potential targets for future drug treatments, in addition to the targeting of amyloid itself.

When, where and how does Alzheimer's disease start?

A summary of the recent studies of pre-symptomatic signs of the disease and the implications for future research

This article is a plain English adaptation of an article written in The Lancet Neurology by Professor Nick Fox.

Professor Fox is a researcher at the Institute of Psychiatry, University College London, and is co-chair of Alzheimer's Society's expert Research Advisory Committee. His previous research has included pioneering work in the development of Magnetic Resonance Imaging (MRI) brain scanning for the diagnosis of dementia.



Biomarkers, either in the blood, cerebral spinal fluid (CSF) or related to brain imaging, could be important for our understanding of Alzheimer's disease, when it begins and how it progresses. They have the potential to tell us the order in which changes occur, and how changes can cause others. This is especially relevant now, as many trials are pointing towards earlier intervention with new drugs as a way to achieve better outcomes with new Alzheimer's disease drugs.

A recent study, published in Lancet Neurology, looked at young adults aged 18–26 from a large family in Columbia that carry a mutation on the PSEN1 gene. This mutation results in the development of early-onset Alzheimer's disease, usually in the

person's 40s, and is dominantly inherited – one copy will cause the disease, so the child of a parent with the mutation has a 50 per cent chance of inheriting the mutated gene and so developing Alzheimer's disease themselves. The study looked at the difference between those young adults with and without this mutation, comparing findings from blood plasma and CSF.

The amyloid-beta peptide that clumps together to form amyloid plaques was found at a higher concentration in the plasma and CSF of the gene carriers than the non-carriers, even this long before symptoms are likely to appear.

Amyloid-beta levels have been found to decrease in CSF of people with Alzheimer's disease as amyloid plaques form, which may be a helpful diagnostic marker; it is thought that the amyloid-beta levels decrease as they begin to form plaques, leaving less amyloid-beta 'free' to enter the CSF. But why did the people with the genetic mutations have *increased* levels, many years before symptoms developed?

This could be related to the type of amyloid-beta produced – the type that was elevated in this study, and is reduced in people with amyloid plaques in their brain, is 42 amino acids long – and so is called amyloid-beta 42 (A β 1-42). Laboratory studies have shown that this type of amyloid-beta is increased relative to amyloid-beta 40, which is less prone to forming amyloid plaques. The increased concentrations of amyloid-beta 42 in the gene carriers, compared with the non-gene carriers, suggest that the production of amyloid-beta 42 is greater in those with the gene.

A question that this study did not answer is whether the amyloid-beta 42 levels have always been higher in these individuals, or if there was a point when they increased. As amyloid-beta 42 CSF levels are decreased in people with genetic mutations who have plaques in their brain, the levels of amyloid-beta 42 in these participants will fall – but this study does not tell us when.

A larger study with young adults, of the same age and from the same extended family, looked at

MRI scans of individuals both with and without this genetic mutation. It found that those with the gene had signs of reduced grey matter volume, and were showing signs of dysfunction in the synapses that connect neurons. However, the amyloid-beta 42 CSF levels in similar family members had not yet fallen, and other studies have suggested that there are no plaques present within the brain at this stage. If these changes are not related to the brain's development in these individuals, this questions what scientists have previously thought about the development of Alzheimer's disease. These results suggest that neurodegenerative changes occur a long time before amyloid plaques are formed; the present hypothesis is that the amyloid plaques occur before, and are a cause of, neurodegeneration. In addition, the results suggest that neurodegeneration occurs a lot longer before symptoms occur than any previous studies have shown.

As with any single, relatively small study, these results should be treated with caution; they are a reason to investigate further, and may not be found to be generalisable to people with sporadic, rather than inherited, Alzheimer's disease. If, however, changes in the structure of the brain can be seen this far in

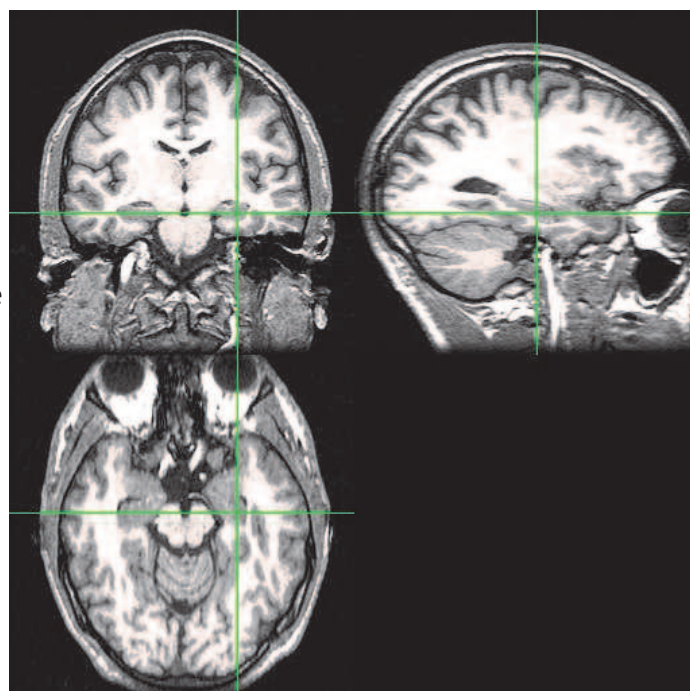
advance of symptoms, this will have great implications for future investigations of Alzheimer's disease and the way that we investigate those changes and potential treatments. For those who believe that treatment should be started before amyloid plaques begin to develop in order to have the best chance of success, this will be made incredibly difficult by the findings that these changes are already present in young adults.

It may be that findings such as these open up the potential for longer-term monitoring and measurements of people during a long phase of the development of Alzheimer's disease before

symptoms appear. The balance for future presymptomatic studies, which will be challenging in any case, is between the potential benefits of treating people very, very early in the disease process – ie many years before symptoms – and the greater feasibility of studying people nearer to when their symptoms begin. This balance has great implications for future trials of treatments for Alzheimer's disease.

The reference for the original article is: Fox, N. *The Lancet Neurology*: 11 (12); 1017-1018

MRI scans in young people with a mutation to a gene that causes Alzheimer's disease, PSEN1, showed changes in their brains compared with people from the same extended family without this gene - but are these changes due to pre-symptomatic Alzheimer's disease?



The Research Network

People with dementia and their carers are integral to our grants programme. We believe that they make a unique and valuable contribution to our work. Their knowledge and passion ensures our research funding is allocated to projects that address the real needs and concerns of people with dementia and their carers.

Research Network volunteers:

- set our research priorities
- prioritise and comment on grant applications
- sit on grant selection panels
- monitor ongoing projects funded by Alzheimer's Society
- tell others about the results of research.

If you have been a carer for someone with dementia or you have dementia and are interested in joining the Research Network, please contact Matt Murray, the Research Network Volunteer Coordinator and request an application form, or go online at alzheimers.org.uk/researchnetwork

If you are not a carer or a person with dementia, but you would like to learn more about our research and keep up to date, you are welcome to become a **Friend of Research**. Just fill in the form on the website (above) and you'll receive a monthly copy of the Research newsletter and information on all our research events.



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