Dementia: Catching the memory thief

September 28 2016

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It's over a hundred years since the first case of Alzheimer's disease was diagnosed. Since then we've learned a great deal about the protein 'tangles' and 'plaques' that cause the disease. How close are we to having effective treatments – and could we even prevent dementia from occurring in the first place?

You may have heard of the 'dementia tsunami'. It's heading our way. As our population ages, the number of cases of dementia is set to rocket, overwhelming our health services and placing an enormous burden on our society.

Only, it's not quite so simple. A study published last year by Professor Carol Brayne from the Cambridge Institute of Public Health suggested that better education and living standards meant people were at a lower risk of developing the disease than previously thought and so, despite our ageing population, numbers were likely to stabilise – and could even perhaps fall slightly.

Of course, even this more optimistic outlook does not hide the fact that millions of people worldwide will be diagnosed with dementia each year and millions are already living with the condition. An effective treatment for the 'memory thief' still seems like a distant prospect.

"Dementia isn't one disease: it's a constellation of changes in an individual's brain, with many underlying causes," says Brayne. "Most people, by the time they're in their eighties or nineties, have some of these changes in their brains, regardless of whether or not they ever develop dementia."

For this reason, Brayne believes we need a radical approach to tackling brain health throughout the course of our lifetime, with a greater emphasis on reduction in the risk of dementia achieved through measures in society that are related to better health in general, such as social and lifestyle changes, in addition to the focus on early therapeutic approaches to preventing or treating the disease through a pharmaceutical approach.

By far the most common and well-known form of dementia is Alzheimer's disease. Symptoms include memory problems, changes in

behaviour and progressive loss of independence.

At a biological level, the disease sees a build-up of two particular types of proteins in the brain: fragments of beta-amyloid clump together in 'plaques' between nerve cells, and twisted strands of tau form 'tangles' within the nerve cells. These plaques and tangles lead to the death of nerve cells, causing the brain to shrink.

Clinical trials of Alzheimer's drugs are always going to be difficult, in part because trial participants are patients with advanced stage disease, who have already lost a significant number of nerve cells. But Professor Chris Dobson, who recently helped secure £17 million from the Higher Education Funding Council for England for a new Chemistry of Health Building, including the Centre for Misfolding Diseases, believes that most of the trials to date were destined to fail from the start because of a fundamental lack of understanding of the mechanisms that lead to Alzheimer's.

Understandably, most of the researchers tackling Alzheimer's approach the disease as a clinical – or at least a biological – problem. Dobson instead sees it as also being about chemistry and physics. He argues that the protein tangles and plaques – collectively known as aggregates – are demonstrating a physical property similar to the way in which crystals precipitate out of, say, salty water: all they need is a 'seed' to kick off the precipitation and the process runs away with itself. "In essence," he says, "biology is trying to suppress molecules behaving in a physical way." For his contributions, Dobson has been awarded the 2014 Heineken Prize for Biochemistry and Biophysics.

In 2009, Dobson, together with colleagues Professors Tuomas Knowles and Michele Vendruscolo, published a study that broke down the aggregation process into a combination of smaller steps, each of which could be tested experimentally. It became apparent to the team that

drugs were failing in trials because they were targeting the wrong steps. "And this is still happening," says Vendruscolo. "Companies are still putting small molecules into clinical trials that, when we test them using our methods, we find stand no chance."

They believe there may be a role to play for 'neurostatins', which could do for Alzheimer's what statins already do to reduce cholesterol levels and prevent heart attacks and strokes. In fact, they may have already identified compounds that might fit the bill.

Professor Michel Goedert from the Medical Research Council Laboratory of Molecular Biology admits that there is a gap between our understanding of Alzheimer's and our ability to turn this into effective therapies.

"We know much about the causes of inherited forms of Alzheimer's disease, but this knowledge has so far not led to any therapies," he says. "It's clear now that abnormal protein aggregation is central to Alzheimer's disease, but we don't know the mechanisms by which this aggregation leads to neurodegeneration." Goedert himself played an instrumental part in studies that implicated the aggregation of tau protein in Alzheimer's disease and other neurodegenerative diseases, work that led to him being awarded the 2014 European Grand Prix from the Paris-based Foundation for Research on Alzheimer's Disease.

"I don't think we should talk of a cure," says Goedert. "At best, we will be able to halt the disease. Prevention will be much more important." Part of the problem, he says, lies in the fact that there is no absolute way of identifying those at risk of developing Alzheimer's disease.

The market for an Alzheimer's drug is massive, which is why pharmaceutical companies are racing to develop new drugs. Goedert doesn't believe we will ever find a single 'magic bullet', but will need to

use combination therapies – in the same way that we treat other diseases, such as HIV – with each drug targeting a particular aspect of the disease.

Professor David Rubinsztein from the Cambridge Institute for Medical Research agrees with Goedert that we need to look at preventing Alzheimer's rather than just focusing on treating the disease. He, too, believes in the concept of neurostatins. "These compounds would be safe, well tolerated by most people and generally good for you; you could take them for many years before the onset of disease," he says. "Then we wouldn't need to worry about identifying people at highest risk of the disease – everyone could take them."

Rubinsztein is the academic lead for Cambridge's new Alzheimer's Research UK Drug Discovery Institute, part of a £30 million Drug Discovery Alliance that also includes the University of Oxford and University College London. This state-of-the-art institute will fast-track the development of new treatments for Alzheimer's disease and other neurodegenerative diseases. In particular, the Alliance will look at promising drug targets, assess their validity and develop small molecules that target them. These could then be taken up by pharmaceutical companies for clinical trials, removing some of the risk that results in most 'promising' drug candidates failing early on.

Rubinsztein is optimistic about our chances of fighting Alzheimer's. "If you could delay the onset of Alzheimer's, even by three to five years, that discovery would be transformative and massively reduce the number of people getting the disease," he says. "We're not asking to stop the disease, just to delay it. It's really not such a big ask."

Provided by University of Cambridge