Dispelling myths about Alzheimer’s disease

Twenty-one years of OPTIMA

Alzheimer’s disease (AD) has been called the silent epidemic: there are about 500 new cases every day in the UK and the world-wide prevalence has been estimated to be 36 million in 2010, which will rise to about 115 million in 2050. Research is the only answer to this huge challenge.

Research into AD in Oxford began in the early 1980’s with pioneering studies by Margaret Esiri, Gordon Wilcock and Tom Powell in the Departments of Neuropathology and Human Anatomy. These studies applied quantitative analysis to histopathological markers in the brains of patients who had been fully assessed in life, so allowing correlations to be drawn between cognitive deficits and pathology. At the same time, animal experiments in the Department of Pharmacology showed that the acetylcholinesterase of cerebrospinal fluid (CSF) was not derived from blood plasma but was secreted from neurons in the brain. It was logical to see if the recently discovered loss of cholinergic neurons in the brain of AD patients was reflected in a decreased level of acetylcholinesterase in CSF – and it was. Thus began collaboration between Margaret Esiri and myself which led to the setting up of the Oxford Project to Investigate Memory and Ageing (OPTIMA) in 1988. My co-founders were Margaret Esiri, Elizabeth King and Kim Jobst. What we originally set out to do was see if the molecular forms of acetylcholinesterase in lumbar CSF could be used as a diagnostic test for AD. To do this, we needed a longitudinal, clinico-pathological study where CSF was taken in life and patients and controls were followed through to autopsy and histopathological diagnosis; that is essentially what OPTIMA is. A special feature of OPTIMA is that it is run by the nurses; for 20 years the senior nurse and operations manager was Elizabeth King. Elizabeth taught us that if we want co-operation from our participants we have to give them something back in the form of support, care and education. This enlightened approach is one of the main reasons why OPTIMA has an autopsy rate close to 90% and why in 21 years only some 45 participants out of more than 1,100 have withdrawn.

When OPTIMA began, views about AD were dominated by two dogmas: first, that it is an inevitable part of normal ageing; second, that it is mainly determined by our genes. OPTIMA has played an important part in dispelling these myths and we now believe that AD is a slowly developing multifactorial disease with a host of non-genetic risk factors interacting with some susceptibility genes. (The familial varieties with autosomal dominant genes are very rare and only occur in patients with early-onset of symptoms.) The challenge now is to identify those non-genetic risk factors that can be modified and to carry out clinical trials to see if modifying them does indeed slow down the progression of the disease.

OPTIMA’s first challenge was to find ways of diagnosing AD in life and of following the progression of the disease. We began life in a small office in the Clinical Neurology corridor in the Radcliffe Infirmary, not far from the Radiology department. Two radiologists were very important in our early work: Andy Molinueux and Basil Shepstone. Margaret Esiri had shown that the part of the brain with the densest accumulation of neurofibrillary tangles in AD was the medial temporal lobe, but this is hardly visible on the standard axial CT scan. Andy Molinueux changed the angle of the scanner so that the long axis of the temporal lobe was revealed. By 1992, we had enough cases to autopsy to show that CT scans in life of patients dying with AD showed a highly significant thinning of the medial temporal lobe compared with age-matched controls such that it was a valuable aid to diagnosis; the result was a paper in The Lancet that stimulated world-wide adoption of imaging the medial temporal lobe in dementia. The temporal lobe oriented CT scan also allowed us to follow disease progression: we measured the thickness of the medial temporal lobe each year in AD patients and in volunteer controls. I well remember when we decoded the results in 1994: it was around midnight, but I called Kim Jobst and told him that in AD patients the medial temporal lobe shrank at almost ten times the rate in controls. We realised that, contrary to dogma, AD could not simply be an acceleration of normal ageing but must follow some catastrophic event in the brain. In other
words, it was a true disease and so we could look for the causes without having to unravel the causes of normal ageing. The Lancet accepted our paper, but did not like the use of ‘catastrophic event’ in the title. We now had a tool to follow the progression of the disease independent of any clinical assessment.

Basil Shepstone is an expert in nuclear medicine and in 1989 he told us that he could easily diagnose AD using SPECT to study regional cerebral blood flow. We were sceptical, so he offered to cover the cost of the first 50 subjects scanned. He was right: reduced blood flow in the posterior parieto-temporal cortex was indeed a characteristic of patients who had histopathologically-confirmed AD. Because we had also scanned the same patients with temporal lobe CT, we were able to show that a combination of thin medial temporal lobes and the neocortical SPECT perfusion deficit gave a highly accurate diagnosis independent of any clinical assessment. More recently, Kevin Bradley used the SPECT scans taken at different times during disease progression to create templates that related the scan image to the pattern of distribution of neurofibrillary tangles after death. This important discovery, published in Brain, was awarded the new investigator Neuroimaging Prize by the American Alzheimer Association in 2004, the first such award outside America. Another discovery arose from the use of multi-modal neuroimaging: we realised that the perfusion deficits in the neocortex were related to the degree of atrophy of the medial temporal lobe and we proposed the hypothesis that the neocortical changes were a consequence of disconnection of these areas from the medial temporal lobe.

In a seminar at the Clinical Trial Service Unit in 1995 I described our finding of rapid atrophy of the medial temporal lobe in AD and suggested that it may be the consequence of a vascular event in the brain.

Afterwards, Robert Clarke came up to me and asked if we had thought of looking at plasma homocysteine levels in our subjects, because homocysteine was a recently established risk factor for vascular disease. We soon established collaboration with the leading laboratory in this field, directed by Helga Refsum in Bergen, and within 6 months we had the answer: plasma homocysteine levels are raised in patients who have confirmed AD. Homocysteine levels are mainly determined by folate and vitamin B12 status and so it was not surprising to find that the levels of these two vitamins were lower in AD. But none of the patients was classically vitamin deficient: the levels were in the low-normal range. This may be OPTIMA’s most important discovery, but it took a long time to convince the world (charted in the Channel 4 film, ‘Assault on the Mind’). Eventually, the paper was published in Archives of Neurology in 1998 and was selected by the American Medical Association as one of the two most important papers of the year. It is the fourth most cited paper in the journal and has to date been cited more than 700 times. The paper is important because homocysteine is one of the first readily modifiable risk factors for AD. Levels of plasma homocysteine can be lowered by supplements containing folic acid and vitamin B12 and so trials can be done to see if these vitamins can slow down the progression of the disease or, better, prevent the disease from developing. With our former Clinical Director, Robin Jacoby, OPTIMA has just completed a pilot randomised trial of the second type (VITACOG) in which 220 volunteers over 70 with memory problems were recruited in Oxford. The end-point in the trial was the rate of shrinkage of the brain assessed by serial MRI scans over two years. If this trial is successful, it will justify much larger trials to see if the vitamins will slow conversion from cognitive impairment to AD.

I have given a highly selective and personal account of OPTIMA, but would like to end by mentioning just a few of OPTIMA’s other important achievements.

- Creation of a biobank of > 30,000 samples of blood, DNA, CSF, urine and brains from well-characterised participants
- Demonstration of episitis, the interaction between two susceptibility genes, in the risk of AD
- Aberrant entry of neurons into the cell cycle in AD may precede neurodegeneration
- Low-normal vitamin B12 levels are associated with faster rate of atrophy of the brain in normal elderly (see Figure)
- Impaired performance on two cognitive tests can predict when normal elderly will become cognitively impaired over a period of up to 20 years

The achievements of OPTIMA depend crucially on the ability to follow participants for a long period, until they die. Few other projects in the world have managed to do this in so many people with such detailed assessments in life. Over a period of 21 years OPTIMA has created an international reputation and has helped to dispel the myths about AD. We are now confident that this disease can be tackled and that it will eventually be possible to prevent many from developing one of mankind’s cruellest diseases.

In 2008 I was very pleased to hand over Directorship of OPTIMA to Professor Gordon Wilcock, who is ably supported by Sharon Christie (Senior Nurse and Operations Manager) and Ellen McCulloch (Clinical Trials Manager). Over the years, OPTIMA has been very fortunate to receive financial support from a wide variety of sources, industrial, MRC, charitable and personal donations. Our main supporters have been Bristol-Myers Squibb, Merck & Co. Inc, MRC, and the Charles Wolfson Charitable Trust. OPTIMA is a founding member of the Alzheimer’s Research Trust network of UK centres. Further information can be found at: http://www.medsci.ox.ac.uk/optima

A. David Smith, Professor Emeritus of Pharmacology, Founding Director of OPTIMA