The Oxford Parkinson’s Disease Centre (OPDC) has been launched following the award of a large grant by the UK Parkinson’s Disease Society. The generous £5 million Discovery Award is funded by the Monument Trust, one of the Sainsbury Family Trusts.

The grant will enable us to study the earliest pathological changes in Parkinson’s disease in order to facilitate earlier diagnosis and discovery of new treatment targets that may prevent, halt or reverse disease progression. Although tremendous progress has been made over recent years, it is still not clear what causes progressive dysfunction and death of vulnerable cells in Parkinson’s and how best to model this process to test new drugs.

The OPDC therefore combines a “back-to-basics” approach of laboratory-based neuroscience research with clinical studies of a large cohort of people in the Thames Valley developing, or at risk of developing, Parkinson’s disease.

Recent advances in the understanding of genetic risks for Parkinson’s disease provide clues about possible triggers of the disease. The next step is to better understand how these apparently diverse genetic factors lead to a common disease process, namely loss of specific cell groups in the brain and abnormalities of a small molecule called alpha-synuclein, believed to be central to the pathology of Parkinson’s.

The direct study of healthy as well as diseased human brain tissue is crucial for this work, as we need to understand how these Parkinson’s disease genes function. Identifying a set of risk genes from a blood test does not tell us how they contribute to the disease in the brain. We will apply new techniques to study gene expression and its regulation in Parkinson’s and control brains from The Thomas Willis Oxford Brain Collection and the UK Parkinson’s Disease Society Brain Bank in London.

Another OPDC project will rely on brain tissue donations, too. We will use high-resolution imaging techniques developed in Oxford on post-mortem brains to better understand the cellular pathology that underpins abnormal MRI scans in Parkinson’s. This research will allow us to better define scanning sequences that ultimately can be used in the clinic to follow disease progression and response to any new treatments.

You can read more about the OPDC here: http://opdc.medsci.ox.ac.uk, and www.parkinsons.org.uk.

(Olaf Ansorge)
The Outreach Coordinator for the Autism Brain Bank

The development of the Brain Bank for Autism (which is hosted in Oxford as part of the Thomas Willis Brain Collection) is supported by an Outreach Co-ordinator, Brenda Nally, who promotes it both to the autism community in the UK and to the general public.

If there is more awareness of the need for brain donation as the basis for research, both the pledges to donate and the post mortem donations made should increase. The public clearly needs greater access to information about the value of brain banking in the research process and the autism community also needs more focused information about the potential value of the research to people with autism and to their families. Early in 2010, an open meeting in Oxford’s St Hugh’s College will enable representatives of autism organisations in the UK to learn more about the Brain Bank for Autism. Dr Karla Miller will contribute by describing the initial project on brain imaging, which is being carried out at the University’s FMRIB unit (FMRIB = functional magnetic resonance imaging of the brain).

A film about the Brain Bank for Autism, made with the support of Oxford’s Media Production Unit, will also be made available to each representative who attends. The Brain Bank for Autism gathers clinical information about each donor, which will inform the research findings, and the donor’s family is closely involved in this process. It is seen to be of fundamental importance to work in partnership with families of donors and to give information about the work of the brain bank and about developments in this area of research to those who have registered a pledge to donate. All of the next of kin of the initial donors have described the experience of donation as positive and some have been active in their support and promotion of the research programme.

A website has been developed (www.brainbankforautism.org.uk) that provides information and the means both to register support for the research programme and to pledge to donate to it. A free helpline also enables callers to discuss their queries and concerns. The Outreach Co-ordinator trains and supports helpline staff to respond to calls. The evidence so far has shown that many more people prefer to gain information from the use of the website than from personal contact through the helpline.

As the UK Brain Banks Network takes shape during 2010, the helpline may be incorporated in a much wider initiative and so may be more extensively used.

We are very grateful to anyone who is supporting this initiative.

(Brenda Nally, Brain Bank for Autism & Related Developmental Research)

21 Years of OPTIMA: Dispelling Myths about Alzheimer’s

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 AD brain 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. What we originally set out to do was to 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 multi-factorial disease with a host of non-genetic risk factors interacting with some susceptibility genes. The challenge now is to identify those non-genetic risk factors.

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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. 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.

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 (single photon emission CT) 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 pathologically-confirmed AD. Because we had also scanned the same patients with 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.

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**What are Brain Minicolumns and what can they tell us?**

Just as a geologist can uncover the processes by which the Earth has formed by examining the rocks around us, so we can study the surface layers of brain structure to reveal how it has developed and evolved. The brain’s surface is formed by the cerebral cortex where most of the brain cells (neurons) are found. This is where the connections are made that enable us to think.

Very early in development, brain cells migrate up to the surface of the brain, forming the cortex by stacking up on top of each other in columns. These are described as “minicolumns” (figure). Each minicolumn acts as a miniature circuit to process information. When mature, the horizontal spacing between the minicolumns is only about 0.05mm, however the number of these minicolumns and the spacing between them determines the overall size of the brain surface.

It is well known that humans have evolved relatively large brains compared to other animals and this is thought to be the basis for human intelligence. One of our projects in Oxford is using the TWOBC to compare the minicolumns in the human brain with those of our nearest primate relative, the chimpanzee. We are investigating the minicolumns in areas of the brain that perform language processing and other complex cognitive functions. So far the evidence shows that human minicolumns are wider, allowing for more connections. They are also asymmetrical in humans, wider on the left, whereas in chimpanzees they are symmetrical: the difference may relate to the fact that language is processed in the left hemisphere in most humans.

We are also applying minicolumn analysis to human pathology. In normal ageing we have found that minicolumn thinning occurs, and in autism there seem to be too many minicolumns so that there is insufficient space between them. Thus, while geologists study the Earth’s crust to infer lessons regarding climate change, we study the cortex of the brain to better understand how subtle pathology occurs. (Steven Chance, University Research Lecturer)
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 findings and suggested that they 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 the progression of the disease or, better, prevent the disease from developing. We are currently analysing the outcome of such a trial (VITACOG) in which 220 volunteers over 70 with memory problems were recruited in Oxford.

I have given a highly selective and personal account of OPTIMA, and would like to end by reiterating how 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. (David Smith, Professor Emeritus of Pharmacology, Founding Director of OPTIMA)

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As we are currently not continually funded by a large strategic grant, we welcome charitable donations, however small, to support our work. If you are interested in supporting us, please contact us at the above address.

(Olaf Ansorge, Margaret Esiri)