The Brains for Dementia Research Initiative

The Thomas Willis Oxford Brain Collection has long had an interest in supporting research on dementia. This has mainly been in the context of the OPTIMA project (Oxford Project to Investigate Memory and Ageing), a 20-year longitudinal study of dementia in which patients with dementia, or incipient dementia, have been seen at regular intervals for psychological tests, medical examination, brain imaging and blood tests through the course of their illness. A high proportion (at least 80%) of these people generously consented to brain donation after their death as they understood the value that brain donation has for furthering dementia research. Feedback was also provided to families about the neuropathological findings on brain examination if this was requested.

OPTIMA has provided a remarkable resource for dementia research not only from studying the brain after death but also from analysis of the blood and other samples taken during the course of disease and from the study of brain imaging in life. For example, recent papers have described studies of the potential value of vitamin supplementation in preventing dementia in the elderly, on possible biochemical diagnostic markers in the cerebrospinal fluid (the fluid that bathes the brain and spinal cord) of Alzheimer’s disease and the value of brain imaging in assessing dementia and its causes in the elderly.

Now there is another source of dementia research and brain donation that is being developed in the Thames valley region. This is the formation of so-called DeNDRoN memory clinics where people who are concerned about memory and other cognitive problems can be referred for assessment. These people will be offered the chance to take part in clinical trials of new dementia treatments or interventions to prevent dementia from developing. In addition, they will be given the opportunity to consent to brain donation after their death. By studying the brain after someone has participated in a new drug trial it may be possible to detect the effect on the brain that a new treatment may have. DeNDRoN memory clinics are being set up not only in the Oxford region but also in other parts of England. Two Alzheimer’s charities, The Alzheimer’s Research Trust and the Alzheimer’s Society, have generously come together to provide financial support for the development of a network of brain collection for research on dementia, called Brains for Dementia Research (BDR). Oxford is one of the centres being supported in this way with a grant to the Thomas Willis Oxford Brain Collection. OPTIMA and DeNDRoN-sourced brains will thus now join a national brain collection to support dementia research. Under full regulation by the Human Tissue Authority this network of brain banks will be able to support use of brain tissue in approved studies throughout the UK and world-wide. In this way it is hoped that tissue-based research into dementia will be given a fillip and yield findings that, in turn, can suggest further novel ways to prevent and treat dementia. Such treatments will come not a moment too soon for, with the anticipated increase in the elderly population in all countries, dementia is set to be a number one priority for health and social services throughout the world.

(Margaret Esiri)

Oxford — A centre for Autism research

A new Oxford University Autism Research Group has been established which is studying clinical and genetic aspects of autism. The group is led by Professors Anthony Bailey and Tony Monaco and has recently contributed to a major study identifying several new genetic autism risk loci. Their work is complemented by a new project, called The Brain Bank for Autism, generously supported by the charity Autism Speaks, and hosted within the Thomas Willis Oxford Brain Collection. This new UK resource will facilitate cutting-edge multidisciplinary research into this complex disease. We will report in future editions of our newsletter on the exciting progress that is made in autism research.

(Elaf Ansorge)
What can neuropathology tell us about Motor Neuron Disease?

Motor Neuron Disease (MND, also known as Amyotrophic Lateral Sclerosis, or ALS) causes progressive weakness of muscles leading to severe problems with mobility, and in some cases speech and swallowing. Eventually, because of failure of the muscles of breathing, most patients with MND will die of their disease. Although it is relatively rare compared to diseases like stroke and cancer, MND is becoming commoner as the population in developed countries lives to a greater age. Neurologists have recognised the disease we call Motor Neuron Disease for about 150 years. During the late 19th century neuropathologists were able to study the brain and spinal cord of patients with MND and to determine that it is primarily a disease of nerves that leads to muscle weakness and wasting rather than a problem within the muscle itself. MND is a neurodegenerative disease, meaning that nerve cells develop and mature normally but, for reasons which are still largely unknown, fail to tolerate some aspect of the aging process.

Neurologists face a difficult challenge in understanding what is happening in neurodegenerative disease. Doctors studying diseases of the blood or liver can look directly in living patients at the tissues relevant to the disease by taking a biopsy or blood sample. Although we can use techniques such as MRI scanning to visualise the brain, this is of limited value in neurodegenerative disease because the important disease processes are occurring at the microscopic level which cannot be directly observed on scans. Taking a biopsy of the brain for research purposes is not possible in routine clinical practice as it carries an unacceptable risk of causing damage and there is no obvious benefit to the patient. This is why studying the brain after death is so important in furthering our understanding of MND. It offers us the only window that we have on what is happening to motor neurons as they become damaged and die.

MND demonstrates a great variation in the site of onset, rate of progression and duration of the illness. An important question is whether this reflects the fact that MND is a single disease with a wide range of behaviour or a number of different diseases. Although this question has not been fully resolved, neuropathological research has demonstrated that the same changes in brain cells occur in most of the different subtypes of MND seen in the clinic. The characteristic pathological hallmark of MND seen under the microscope is the accumulation of protein that is resistant to the normal processes in the cell that clear it. This protein (known, in short, as “TDP-43”) can be recognised as being specific to MND cases because it is tagged with another protein called ubiquitin, fragmented and removed from its normal position in the cell nucleus. In fact, it now appears that MND shares some pathological hallmarks with a particular form of dementia, Frontotemporal dementia (FTD), in which nerve cells accumulate the same insoluble ubiquitin-tagged TDP-43 protein.

The discovery of TDP-43 has been the direct result of neuropathological study of human post mortem tissue from patients affected with MND. It represents the most significant discovery in the field of MND research for over a decade and brings us a significant step closer to a complete understanding of this devastating disease. To test if alterations in TDP-43 are sufficient to cause MND, geneticists set out to screen the gene encoding TDP-43 in a large number of patients with the disease. Remarkably, a small number of patients carry indeed mutations of TDP-43 that are not seen in people without MND. This important finding will now enable us to create new and improved models of the disease in order to test new targets for treatment of this challenging disease.

It is important to appreciate that all of this new information has come because neuropathologists still continue to study the brains of MND patients, 150 years after the disease was first described. New techniques for studying the brain are constantly being developed and this requires new material for study. Patients with MND and other diseases often ask about brain donation after death and, often knowing that the advances from neuropathology may come too late to help them, they receive some comfort from the knowledge that their gift will help alleviate the suffering of patients to come.

(Kevin Talbot and Olaf Ansgor) (Kevin Talbot is a Reader in Clinical Neurology and Director of the Motor Neuron Disease Clinic in Oxford. He also leads a research group investigating the genetics and biology of motor neuron disorders. Olaf Ansgor is lead Consultant of the Oxford Neuropathology Department and co-directs the Brain Collection with Margaret Esiri)

Research update: Progressive Supranuclear Palsy

Progressive supranuclear palsy (PSP) is a degenerative disease of the brain which results in a person having difficulty moving, losing balance and becoming prone to unexpected falls, particularly falling backwards. At the same time a patient will have difficulty looking downwards and become slowly cognitively impaired. The disease appears in the clinic to be very

(continued on next page)
Multiple Sclerosis research in Oxford

Multiple Sclerosis (MS) is one of the most common neurological diseases affecting young adults in the United Kingdom. Although much progress has been made in the diagnosis and management of this disease, its ultimate cause remains unclear.

Oxford has been at the forefront of MS research for many years. One of the strengths of Oxford’s MS research environment is that it draws together a group of clinicians, imaging experts, neuropathologists, geneticists and basic scientists. It is increasingly being recognised that a multidisciplinary approach is needed to understand this complex disease. Close collaboration between these groups is well established in Oxford and supported by the recently created Biomedical Research Centre that promotes rapid translation of new discoveries from the laboratory bench to the bedside in order to maximise any benefit for patients.

The Thomas Willis Brain Collection holds donated tissue from people with MS and also has access to tissue generously provided by the UK MS Society Tissue Bank at Imperial College in London. This tissue is being used in several ongoing research projects in Oxford.

MRI is a very important tool in the clinical diagnosis and management of MS. However, it is not entirely clear how some imaging features relate to specific cellular or molecular changes in the brain tissue or how MS lesions lead to a reorganisation of fibre tracts remote from the actual lesion.

The new project applies cutting edge imaging methods to fresh and fixed post-mortem brain from persons with MS and normal individuals who died without brain disease. Areas of abnormal MRI signal are then studied pathologically.

This approach will allow a detailed correlation between imaging and pathology. Information gained from these studies will inform the development of new imaging protocols for clinical use. For example, it is hoped that these studies will enable us to define imaging parameters that will allow the visualisation of remyelination in vivo.

(Olaf Ansorge)

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similar to Parkinson’s disease but actually has a very different underlying cause. PSP occurs at a frequency of about 10% that of Parkinson's disease, or about 6 or 7 cases per 100,000 with incidence increasing with age and an average age on onset of 63.

As with more common diseases such as Alzheimer's disease the first detailed insights into PSP came from looking at post-mortem brain tissue from patients. It was found that the post-mortem brain of a patient who has died from PSP contains protein aggregations, or neurofibrillary tangles, made of a protein called microtubule associated protein tau (MAPT or tau). In PSP it is known that these tangles are made predominantly of one particular form of the tau protein called 4R tau. However, it is not known why these occur, or why specifically the 4R form of the protein builds up.

Ten years of genetic studies have shown that people who carry one common form of the MAPT gene (called H1) are more susceptible to PSP than people who carry another common form (called H2), which may be protective against neurodegeneration.

My research group is trying to understand how the difference in the forms of the MAPT gene might affect an individual’s susceptibility to suffering from PSP. Recent work by my group studying post-mortem brain tissue from the Thomas Willis Oxford Brain Collection (TWOBC), which we published in 2006 and 2007, showed that the H1 form of the MAPT gene promotes production of 4R tau more than the H2 form does. We suggest that the differing amounts of 4R tau produced by H1 and H2 may be a mechanism which makes carriers of H1 more likely to suffer from PSP. We should also remember that many of us carry two copies of the H1 gene and remain perfectly healthy, and so it is also likely that there are environmental aspects to the disease as well.

Our work into the causes of PSP is in part jointly-funded by two PSP charities: Cure PSP, a charity based in the United States, and The PSP Association Europe, a charity based here in the United Kingdom. We hope that our work will help us understand much better the molecular and genetic mechanisms of PSP to help us identify people at risk from the disease and gain a better understanding of how to develop a therapy.

Oxford is an outstanding place to undertake work into the mechanisms of neurodegenerative diseases and there is a thriving research community. Such work is only possible with the support of brain banks such as the TWOBC.

(Richard Wade-Martins)
(Head, Molecular Neurodegeneration and Gene Therapy Group, Oxford, and member of the Thomas Willis Collection management committee)
Profile: Margaret Esiri — Director of the Brain Collection


At present she is Emeritus Professor of Neuropathology at Oxford University and Honorary Consultant Neuropathologist to the Oxford Radcliffe NHS Trust. Most of her research has been on the pathology of human central nervous system diseases (especially dementia, inflammatory diseases such as multiple sclerosis and encephalitis and schizophrenia) but she has also worked on muscle disease, the subject of her DM thesis, and on experimental models of herpes simplex virus encephalitis and leprosy in animals. She has received many grants to support her work from the UK Medical Research Council, the Wellcome Trust and other medical charities in the UK and USA. With Professors A D Smith and G K Wilcock she is a Director of the Oxford Project to Investigate Memory and Ageing (OPTIMA), a longitudinal clinico-pathological study of dementia. She is a Professorial fellow of St Hugh’s College, Oxford and a Fellow of the Royal College of Pathologists.

For much of her professional life she has worked part-time which has enabled her to spend time in Nigeria, West Africa where her husband had a health clinic for many years in a remote part of the country. This has led to very diverse experiences including the opportunity to carry out some primary clinical care – something a pathologist would never be able to do in this country! She takes much pleasure from the company of her 3 children and 6 grandchildren as well as from her continuing part-time professional work.

(Margaret Esiri)

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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)