

## Department of Neurology

**Director – Professor Stephen Davis**  
**Deputy Director – Dr Peter Hand**  
**Nurse Unit Manager – Corey Swift**

The Department of Neurology is recognized as one of the strongest in Australia and has international recognition for its work in stroke, epilepsy and multiple sclerosis in particular. The Department has active and laboratory research programs, which augment each of the clinical specialised programs undertaken by the department alone and in conjunction with the Department of Neurosurgery. The specialised clinical programs include: Stroke, Epilepsy, Multiple Sclerosis, Parkinson's Disease, Movement Disorders, Neuro-ocular disorders, Neurophysiology, Peripheral Neuropathy and specialized programs in neuroradiology and neurovascular.

### Stroke

#### The Stroke Care Unit at the RMH

The RMH Comprehensive Stroke Centre is the most active in Australia and treats approximately 800 acute stroke patients each year at the RMH. The Stroke Clinic, headed by Dr Peter Hand, has been a great success and it provides a high-quality outpatient service to follow up acute stroke patients. A major research program underpins the clinical service and involves a team of neurologists, neuroradiologists, MRI physicists, statisticians and research nurses and is supported by an NHMRC program grant and the Royal Melbourne Hospital Neuroscience Foundation.

Patients participating in research trials participate in world leading programs in primary stroke care and secondary prevention. "Code Stroke" was introduced to optimise collaboration between Stroke Care Unit and Emergency Department to deliver acute therapies of tPA to patients who have been diagnosed with stroke and are within the therapeutic window for this treatment.

**RMH Comprehensive Stroke Centre**



### Research Themes in Stroke

#### EPITHET (Stroke)

The EPITHET trial, supported by an NHMRC grant, involved 101 patients from 14 participating centres, in Australia, New Zealand and Belgium. This trial tested the hypothesis that imaging of the ischaemic penumbra using MRI could allow selection of patients for thrombolysis with tPA beyond the

accepted three hour clinical window. While other studies have suggested that tPA can be administered to patients with a penumbra beyond three hours, EPITHET is the only randomised controlled trial that has formally test this hypothesis in a prospective design.



Based on the EPITHET dataset, a large number of substudies are being performed to address basic questions about recanalisation and reperfusion in ischemic stroke. We are conducting research into the causes of expansion of hematoma after intracerebral hemorrhage, using novel imaging techniques.

Another study is aimed at better prediction of factors that lead to recurrent brain ischemic events after TIAs and minor strokes.

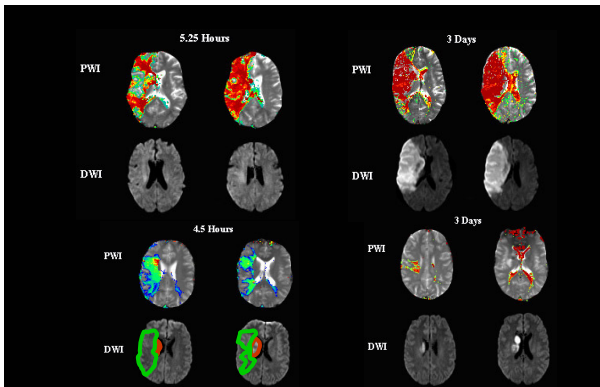
High blood sugar (hyperglycemia) is known to be a major predictor of poor stroke outcomes and a theme of our research in recent years has been to better understand the precise mechanisms of this deleterious effect. We have shown that hyperglycemia in stroke is particularly prominent when the insular cortex is involved. We have explored the interactions between hyperglycemia and various markers of the prothrombotic state after stroke.

The ischaemic penumbra is a region of brain where there is critical reduction of blood flow, but potential viability can be restored with early

treatment. It is widely considered that rapid identification of the penumbra could allow selection of patients for thrombolytic therapy at much later time points than those established in the clinical trials.

The EPITHET trial results were presented in Feb 2008 in New Orleans and published concurrently in Lancet Neurology. We showed that there was increased reperfusion and strong trends to limitation of infarct growth and improved clinical outcomes, confirming our hypotheses and supporting the role for thrombolysis beyond 3 hours.

The RMH conducts many other trials. Professor Davis is a member of the Steering Committees of the Novo 7 program in intracerebral hemorrhage and the recently concluded SAINT program of NXY-059 in acute ischemic stroke. Both of these programs have produced positive trial results in the last 18 months, with two publications in the New England Journal of Medicine.



### Imaging Predictors of Stroke

Research funding supported by the RMH Neuroscience Foundation has been of enormous benefit in our stroke research program over previous years. The overall theme of the current proposed program is the better prediction of outcome after stroke, which has the real possibility of leading to better therapies for stroke patients. In Australia, stroke is the 3rd commonest cause of death, the commonest cause of disability and an enormous burden to patients, carers and the community.

**‘PREDICT’** Prediction in ischemic cerebral transient events – The use of MRI to predict recurrent vascular events in transient ischemic attack (TIA) and minor stroke

Many patients with stroke have warning attacks, or mini-strokes, called transient ischemic attacks (TIA). The goal of Project 1 is to identify those patients who are at high risk of a subsequent devastating stroke, so that therapies can be optimised for these patients. Our research suggests that early subtle changes on brain MRI scans can predict these high risk patients.

Another aspect of this project is to use new blood tests (called biomarkers) which identify chemical factors in the blood that may also help in prediction of high risk patients. This project is supported by the Human Research & Ethics Committee at the RMH and the results should be of great importance to the international stroke community.

**‘ENHANCE’** Enhancement of Hematoma in the Analysis of Clot Evolution: CT angiography in the prediction of hematoma growth in primary Intracerebral hemorrhage (ICH)

**‘EXPANDS’** CT predictors of hematoma growth in primary intracerebral hemorrhage: density heterogeneity and shape

These two projects concern brain hemorrhage, the cause of stroke in about 15% of patients. Patients with brain hemorrhage (where blood vessels rupture) have much worse outcomes than those with ischemic stroke (where blood vessels are blocked by blood clots), with a higher mortality rate. Unfortunately many survivors are destined for nursing home care.

In recent years, a major advance in this field has been the identification that a high proportion of patients within the first few hours after onset of cerebral hemorrhage exhibit further growth of these bleeds within the brain. In fact, our research at the Royal Melbourne Hospital has shown that over 70% of patients show growth of their initial hemorrhage and that this further growth independently predicts worse outcome and increased risk of death.

Our research program is analysing two important predictors of hemorrhage growth. ENHANCE is based on a new sign recently described called the “spot sign”, where an intravenous injection of contrast during a CT scan can actually show leakage of blood out of the blood vessels in the brain and hence indicate ongoing bleeding. We are trying to determine whether the presence of this spot sign at later times over 24 hours predicts further growth. Again, this project is being supported by our Human Research & Ethics Committee at the RMH and has the potential to help identify these patients at high risk of hemorrhage growth and further clinical worsening.

EXPANDS involves an analysis of the shape of the initial hemorrhage (regular versus irregular shapes) and variations in the density of the blood clots in the brain. We predict that more irregular hemorrhages, larger hemorrhages and those imaged early will show a greater tendency to further expansion. The aim again is to identify

these high-risk patients, who are potentially going to exhibit substantial growth and clinical worsening, so that we can use new treatments that make the blood stickier and prevent this further bleeding. Therefore, this research program has great potential to impact on future treatments. This project has also been approved by the Human Research & Ethics Committee at the RMH.

In summary, the research program in both the patients with transient ischemic attacks and cerebral hemorrhage should help in identifying high risk patients for further worsening and allow more focused, aggressive therapy to improve outcomes.

## **Epilepsy**

### **Comprehensive Epilepsy Program**

The Royal Melbourne Hospital Comprehensive Epilepsy Program research is focussed on clinically relevant research. The clinical service has 4 in-patient beds for comprehensive assessment of patients with epilepsy and related disorders, including video-EEG monitoring, neuropsychology, neuropsychiatry and neuroimaging. Over 200 patients per year are admitted. Additionally, 3 specialist outpatient clinics are run focusing respectively on newly diagnosed, chronic, and difficult to treat epilepsy.

Our objectives are to always:

- improve the care and quality of life of patients with newly diagnosed and chronic epilepsy and
- improve clinical quality feedback and practice in the video-EEG monitoring unit.

### **Research Activity in Epilepsy**

We undertook a clinical audit of the number of patients who bit their tongue or were incontinent during inpatient video-EEG monitoring. Tongue biting occurred in 26% of patients who had a convulsive epileptic seizure, but no patient who had a non epileptic seizure. Incontinence occurred in 23% of patients who had an epileptic seizures and 6% of those with a non-epileptic seizure. Data from this audit has been accepted for publication in the leading international epilepsy journal, *Epilepsia*.

The RMH Epilepsy Program conducts a wide range of clinical and basic translational research programs, particularly focused on the areas of new anti-epileptic drug development, brain imaging, neuropsychiatric co-morbidities and evaluating the long-term outcomes of epilepsy and its treatment. Some of the highlights of the clinical research this year have been: Publication in the high impact psychiatric journal, *The British Journal of Psychiatry*, of a large study comprehensively evaluating the incidence and nature

of psychiatric co-morbidities in 319 patients with chronic epilepsy. This is the largest such study published, and documents that these patients have a high incidence of psychiatric disorders (58%), particularly mood disorders, psychosis and personality disorders. This work was conducted in collaboration with the Drs. Sophie Adams and Dennis Velakoulis from Neuropsychiatry. Pharmacogenetic research has derived and validated a multigenic model that is predictive of the outcome of newly treated epilepsy with respect to seizure control, the first such model reported for the treatment of any diseases. This novel model, for which a provisional patent has been lodged, has great scientific and clinical value and is generating significant commercial interest for its potential application as a diagnostic test in clinical practice. A paper reporting will be shortly submitted to a leading general medical journal.

Publication in the leading international imaging journal, *The Journal of Nuclear Medicine*, of a paper reporting a decision tree analysis which evaluates the sensitivity, specificity and cost-effectiveness of clinical algorithms which incorporate FDG-PET in the work-up of patients for epilepsy surgery. This is the first time that decision tree analysis methods has been used to objectively assess the cost effectiveness of different clinical algorithms for the use of investigations in the epilepsy surgery evaluation. The increasing number of different and expensive tests advocated for use in the epilepsy surgery evaluation makes such an evaluation particularly opportune. The results conclusively demonstrate that FDG-PET is cost effective in the pre-surgical evaluation, particularly when employed in patients with a non-localizing or non-concordant VEM and/or MRI result.

- Investigation into the effect of neuropeptide Y-related mechanisms in a genetic model of absence epilepsy.
- The neuropharmacological mechanisms underlying the aggravation of absence seizures by carbamazepine utilising a genetic rat model.
- Development of a mouse model to investigate the mechanisms underlying the adverse weight and bone effects of treatment with the anti-epileptic drug valproate.
- The effect of stress, hypercortisolaemia and early life exposures on epileptogenesis in a rat model of temporal lobe epilepsy.
- Serial functional (PET) and structural (MRI) neuroimaging of changes occurring during epileptogenesis in a rat model of temporal lobe epilepsy.
- Saturation ENU mutagenesis screen for novel anti-epileptic and anti-epileptogenic genes.

- Role of proteases in the mechanisms of acquired limbic epileptogenesis.
- Functional genomics of rodent models of epilepsy.
- Study of clinical, neurocognitive, neuropsychiatric and QOL outcomes following first seizure; evaluating a cohort of about 600 patients who attended first seizure clinic at the Royal Melbourne Hospital.
- Cross sectional and longitudinal study of prevalence and determinants of psychiatric, neurocognitive and QOL issues in people admitted to Video EEG monitoring unit.
- KONQUEST: Study of neurocognitive, neuropsychiatric and Quality of life outcomes with treatment with Keppra versus older standard anti epileptic medication monotherapy in patients who failed their first anti epileptic medication.
- New MRI imaging techniques in subtypes of temporal lobe epilepsy
- Functional imaging (PET @ SPECT) and surgical outcome in temporal lobe epilepsy.
- Investigation of imaging, neurocognitive and behavioural aspects of post-traumatic epilepsy using a rat model.
- Basic pharmacokinetic studies of valproate in rat models of epilepsy.

### **The Effect of Stress and Early Life Experiences on Vulnerability to Temporal Lobe Epilepsy & Mood Disorders**

Anxiety and depression are common co-morbidities in temporal lobe epilepsy (TLE), the most prevalent form of medical refractory epilepsy in the community, occurring in up to 50% of patients. Until relatively recently it had been widely assumed that this was a consequence of the chronic epileptic condition. However, recent evidence suggests that there is a bi-directional relationship, with the psychiatric conditions and stress also acting to aggravate the seizures and even predispose to the development of the epilepsy itself. Conversely there is now emerging evidence of the protective effects of positive early life experiences. Apart from gaining insights into causes of TLE, anxiety and depression, this framework has potential public health relevance suggesting approaches to the eventual primary and secondary prevention of both TLE and its associated psychiatric co-morbidities, a neglected area at present. We are utilizing a rat model that allows investigation of aetiological processes that extend over the lifetime, which is exceptionally difficult to achieve in humans. Retrospective clinical studies, such as case-control studies, although an indispensable research methods, are subject to bias and imprecision when it comes to measuring remote past exposures to stress, abuse, and deprivation. If the results of these experiments are consistent with our hypotheses, a

very strong case would exist for exploring this relationship in human studies. The data would also provide a strong rationale for more aggressive detection and treatment of these psychiatric co-morbidities in TLE patients, in order to potentially modify the progression of the disorder as well as improve the quality of life of sufferers. The results of intervention studies may suggest specific mode of treatment to achieve this.

### **Pharmacogenomics of Anti-Epileptogenic Drugs (Epilepsy)**

Epilepsy is the most common serious chronic neurological disease, affecting up to 3% of the population. Currently treatments for patients with epilepsy, antiepileptic drugs (AEDs), are prescribed essentially on a "trial and error" basis, with little rational basis for the specific AED chosen. Somewhere between 20-40% of patients with epilepsy will fail to have their seizures controlled by the first AED prescribed, and 40% or more will have a significant adverse drug reaction (ADR) – either major or minor. As a result, many patients are subjected to a series of trials of different AEDs and combinations until one is found to be the most effective and tolerated. There are currently a large number of AEDs available in Australia, making this practice extremely costly and exposes the patients to increased risk of suffering a serious ADR which can even on occasions lead to death. The emerging field of pharmacogenomics holds the promise of safer and more effective drug therapy with the potential to individualise and optimise drug therapy, and would be particularly applicable to the treatment of epilepsy. However, in order to make this individualisation of medication prescribing a future reality, prospective clinical information needs to be collected regarding the outcome of AED therapy in individuals that can be then correlated with their genetic information.

Candidate genes for pharmacogenetic testing are those in which there are variations (polymorphisms) that affect AED transport, metabolism, site of action or the immune response. The polymorphism also needs to be carried in the population with a high enough gene frequency to logically explain, or partly explain the frequencies of ADR or pharmacoresistance. An increasing number of studies have attempted to identify such polymorphisms, with many reporting significant associations. However, replication attempts have almost all failed to definitively confirm this association. The most illustrative example of this is with a polymorphism (3435 TT/CC) in the multidrug resistance 1 (MDR1) gene. MDR proteins have been proposed to play a

role in brain transport of AEDs, and genetic variations in these may affect the rate of drug efficacy and side effects. A several high profile publications have reported an association between this MDR1 gene polymorphism with pharmacoresistance in patients with chronic epilepsy, but more recent studies have refuted this. However, almost all studies of pharmacogenomics of AEDs have been limited by multiple confounders and retrospective clinical data. Our research group have initiated an international collaboration that prospectively collects a database of clinical, drug response, adverse drug reaction and genetic information from patients newly treated for epilepsy. Relevant factors that may differ between the centres are examined, including the distribution of genotype frequencies, ethnicity, medication usage and seizure types. This collaboration now has treatment outcomes and genotype correlations from 525 newly treated patients

## **Multiple Sclerosis**

### **Multiple Sclerosis Clinical Research Trials**

The Multiple Sclerosis Unit cares for approximately 471 patients with multiple sclerosis per year at the Royal Melbourne Hospital. The Unit participates in 13 clinical trials of potential therapies for multiple sclerosis. This activity allows our patients access to the latest advances in therapy and keeps medical and nursing staff up-to-date with current trends. Most of the trials have an MRI component which strengthens our links with the Department of Radiology.

Apart from the inpatient and outpatient care of patients with multiple sclerosis, the MS Unit has a major commitment to the conduct of randomized clinical trials of new medication for multiple sclerosis. This activity allows our patients access to the latest advances in therapy and keeps medical and nursing staff up-to-date with current trends. The trials also have an MRI component which strengthens our links with the neuro-radiologists within the hospital. At present we are participating in international multi-centre trials in collaboration with Biogen-Idec, Bayer-Schering, Merck-Serono, Sanofi-Aventis, GSK, Genzyme and Novartis.

### **Ausimmune**

A prospective Australian multi-centre study of environmental factors in first demyelinating event: a case control study.

We have recruited over 300 patients to this study and have established that there is a strong latitudinal gradient of incidence and we are now interrogating the environmental factors that drive susceptibility at both the individual and community level.

### **Vitamin D in Multiple Sclerosis**

A prospective randomised double-blind study assessing the efficacy of high dose Vitamin D in limiting disease activity as assessed primarily by MRI in MS.

### **Gene expression profiling in first demyelinating events.**

A prospective analysis of the genes expressed by CD3 positive lymphocytes of patients both during their first demyelinating event and after recovery compared to the profile exhibited by cohorts.

### **ANZGene**

A multicentre study of 2,000 patients designed to assess the genetic determinants of clinical course, concentrating on patients with primary progressive and overt relapsing-remitting disease.

The role of MRI in predicting visual dysfunction in chronic optic neuritis

There is a compelling need to develop new therapies for multiple sclerosis that either protect the nervous system from immune damage or which assist in its regeneration. This requires not only candidate treatments but also robust mechanisms by which to test them in clinical trials, mechanisms that unfortunately are not, as yet, available. We have posited that detailed study of optic neuritis, one of the common presenting features of multiple sclerosis, might address this need. To establish whether this is the case, we have analysed the relationship between changes on magnetic resonance imaging (MRI), in particular those defined by diffusion weighted imaging and assessments of optic nerve volume, with changes in visual function, as assessed by multifocal visual evoked potentials (mfVEPs) after optic neuritis. We found that there were significant abnormalities in MRI and mfVEP measures in nerves affected by past optic neuritis in comparison with controls. In particular, variance in mfVEP amplitude asymmetry was explained by a linear model combining fractional anisotropy as a diffusion-based measure and nerve volume asymmetry measures ( $R=0.80$ ). These results suggest that MRI is likely to provide useful outcome measures in studies assessing the efficacy of neuroprotective therapy in MS and other neurodegenerative diseases designed to maintain axonal integrity.

### **MS Base**

An international, online registry and platform for collaborative outcomes research on multiple sclerosis.

Since 2004, the Royal Melbourne Hospital Neuroscience Unit has played a major leadership role in the development and implementation of MSBase ([www.msbase.org](http://www.msbase.org)), the only international web-based MS outcomes database. MSBase collects anonymised physician-generated key outcomes data from MS patients worldwide, and currently contains more than 7350 patient datasets from 57 MS centres in 21 countries. In 2007, the number of patient records almost doubled, and growth has remained linear for the first three months of 2008. Data quality remains exceptional, with updates received an average every 5 months, and 90% of records updated at least annually. The MSBase scientific leadership group conducts central, whole dataset outcomes analyses but also allows physicians in individual centres to collaborate with each other in a "substudy" functionality, which is now hosting six ongoing physician-initiated multi-centre epidemiological outcomes studies. MS Base has initiated a 'seen from onset' cohort study, which has now recruited over 1250 patients from 27 centres and is the largest study of its kind in the world.

### **Movement Disorders and Parkinson's disease**

The Movement Disorders research program is focussed on clinically relevant research that will lead to improved patient care and to enhance quality of life of patients with Parkinson's and other movement disorders.

Current initiatives include undertaking to investigate the prevalence and impact on quality of life of pain syndromes in Parkinson's disease, the role of continuous dopaminergic stimulation in reducing the incidence of the neurobehavioral effects of medications, the development of a deep brain stimulator program for the management of Parkinson patients and other movement disorders, and enhanced care of patients with a variety of spasticity disorders.

### **Parkinson's Disease Research**

A project is currently being established in collaboration with Assoc Prof Stephen Gibson of National Aging Research Institute and Dr Michael Farrell of the Howard Florey Institute to examine the impact of pain on quality of life and functioning in Parkinson's disease. In a separate study, the effect of continuous dopaminergic stimulation on other non-motor symptoms in Parkinson's patients will be examined.

In addition the phenomenology, neurobiology, impact on quality of life and management of movement disorders that occur with multiple sclerosis will be examined in a longitudinal study.

In a separate study the role of physiotherapy and triggers for seeking treatment in patients with dystonia will be examined.

### **Clinical Neurophysiology and Peripheral Neuropathy**

The Department of Clinical Neurophysiology has a major commitment to the conduct of randomized controlled trials of new treatments for a variety of peripheral neuropathies. Particular areas of interest have been the diabetic neuropathies, chemotherapy induced neuropathies and the demyelinating neuropathies.

An important role of the department is in the safety monitoring of new drugs (either TGA approved or research related) with potentially neurotoxic side effects. Adverse events such as peripheral neuropathy or optic neuropathy can be identified at a subclinical stage using neurophysiologic techniques.

Current initiatives include enhancing the assessment of small fibre neuropathies with utilization of quantitative sensory testing, and development of further tests to evaluate autonomic function.

### **Neurovestibular Program**

The Ocular Motor and Vestibular Research Laboratory investigates, voluntary and reflexive motor control using the ocular motor system as a model motor system. Taking advantage of the widespread ramifications of control structures within the cerebral hemispheres, the cerebellum and the brainstem, as well as the wealth of literature on the function of various structures, the laboratory is specifically interested in the cognitive processing of information involved in the selection and generation of movements. In particular, we are investigating the competition and resolution of selection processes for willed (top down) processes and reflexive (bottom up) processes.

A clinical Service is now being provided with clinical assessment being undertaken within the structure of the Neuro-ophthalmology Clinic. Diagnostic services are expanding within the Department of Neuro-ophthalmology and we are now looking to expand that service.

A main direction of the clinical program remains investigation of the influence of cognitive set and cerebral hemispheric disease on fundamental reflexes such as the vestibular reflex. We hope to be able to integrate this with specific rehabilitation programs

**Assessment of ocular motility: metrics and the effect of disease on the cognitive functions determining generation of appropriate eye movements.**

In this study we are assessing patients with proven multiple sclerosis. We perform the standard neurological and neuro-ophthalmic examinations. All consenting patients then undergo a standard battery of neuropsychological tests to exclude any frank cognitive dysfunction, before undergoing a comprehensive quantification of ocular motor function. The results are then compared with those of normal subjects and are also compared with standard evaluation of dysfunction in MS, the EDSS, to determine the sensitivity of the technique. This is a preliminary prior to undertaking a longitudinal study.

**Ocular motor function and cognitive influences in a group of adolescent patients with autism.**

There have been findings of motor disorder in autism suggestive of cerebellar dysfunction. This study looks at a comprehensive assessment of ocular motor function in this patient group to try and document motor performance and establish patterns of abnormality that might provide further insights into the nature of the pathological processes at work.

**Ocular motor function and cognitive influences in a group of adolescent patients with Asperger's syndrome.**

**Research Themes in the Neurovestibular Program**

Our main direction remains the investigation of attention and hemispheric influences on vestibular, smooth pursuit and saccadic eye movements in normal subjects and patients with extrapyramidal disorders as well as autism and Aspergers.

We have extended our studies to include establishing a rating scale for motor performance, utilizing the unique nature of the ocular motor system in that it utilizes substantial parts of motor cortex, has extensively ramified connecting pathways and also utilizes a substantial part of brainstem as the ocular motor generator. We are now commencing trials in order to validate its utility in assessing progression in neurological disease.

**Current Funding Sources**

- Biogen-Idec
- Novartis
- GSK
- NINDS
- Bayer Schering
- Genzyme
- NH&MRC Program Grants for Stroke, Epilepsy and Multiple Sclerosis
- NH&MRC Fellowships in Stroke, Epilepsy and Multiple Sclerosis
- Royal Melbourne Hospital Neuroscience Foundation
- Sanofi-Aventis
- Serono
- UCB Pharma

