Basic Science
Clinical Interface

First Annual
Stroke Research Retreat

August 31st to September 1st, 2002
Warrenmang Vineyard, Moonambel

G.A. Donnan (Editor)
First Annual Stroke Research Retreat

2002

‘Basic Science Clinical Interface’

Facilitator
Professor Frederick A O Mendelsohn
**Professor Frederick A O Mendelsohn**

**Position and institution:** Director, The Howard Florey Institute of Experimental Physiology and Medicine, R Douglas Wright Chair of Experimental Physiology and Medicine, University Melbourne.

**Contact details:** Email: faom@hfi.unimelb.edu.au

**Qualifications:** MD, PhD, FRACP

**Research experience:** 1996 - Honorary Consultant Physician, Austin & Repatriation Medical Centre, 1992-96 - Scientific Director, Positron Emission Tomography Centre, Austin Hospital, 1990-96 - Personal Chair in Medicine, University of Melbourne

**Current research interest:** Chemical Neurotransmission, Neuropeptides, Memory

**Relevant publications:**


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Boehringer Ingelheim Pty Ltd (Jim Panagiotidis & Rebecca Joselin)

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Schering Australia Pty Ltd (Mathew Richards)

Aventis Pharmaceuticals Pty Ltd (Stuart Hocking & Roy Gustini)
The National Stroke Research Institute was established in 1994 at the Austin Hospital. It is now in its eighth year and has grown from a small group of about ten researchers up to its current level of about 50 staff members in total. As the only institute focused on stroke research only, it was important to develop a “vertically integrated” approach to solving the problem of stroke with a number of divisions which could readily interact. Hence we now have a Basic Science, Neuroimaging, Ultrasound, Clinical Trials, Epidemiology and Public Health Divisions. Further expansion occurred when our outstanding collaborating centres from the Royal Melbourne Hospital (Professor Stephen Davis), the John Hunter Hospital in Newcastle (Dr. Chris Levi) and the Royal Perth Hospital (Professor Graeme Hankey) became involved. The quality of research being performed across all centres is exceptional. However, like all programs there is always a need to review and set new directions. This is the focus of our Retreat activities.

This year we are fortunate in having Professor Frederick Mendelsohn AO, Director of the Howard Florey Institute, as our facilitator. He has an outstanding record in basic research and, as a clinician, has an appreciation of the broader range of research issues which confront us today.

We have been fortunate in the support of our sponsors from the pharmaceutical industry who are increasingly playing an important role in collaborative research in this country as well as others internationally. I thank them for their involvement and look forward to their continuing support.

The format of the Retreat is designed to involve all participants in discussion after fairly brief presentations to set the background. Spirited discussion often brings new ideas to the table and a focus for our future efforts.

Welcome to the Retreat and I look forward to your involvement.

GEOFFREY A. DONNAN
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POST-RETREAT REPORT FROM FACILITATOR PROFESSOR F.A.O. MENDELSON

Thank you for inviting me to participate in this symposium. I am struck by the advances in stroke management, sophisticated neuroimaging and the pleasing results of thrombolysis, on one hand, and the failure of multiple trials employing a range of putative neuroprotectant drugs, on the other.

The glorious surrounds of Warrenmang Vineyard here in the Victorian Pyrenees provides an excellent opportunity to reflect on what has been achieved, what needs to be done and possible ways forward. Will the much needed progress in neuroprotection come from dramatic breakthroughs in understanding the pathophysiology of ischaemic neuronal damage, or from gradual advances employing our current knowledge?

I well remember Peter Bladin seeking Austin Doyle’s approval to set up a stroke unit in 1978; Austin foresaw its potential and, like Peter’s other far-sighted ideas, he supported it strongly. The general physicians, however, were not so keen, but today the benefits are obvious to all.

The first staff member was a young Research Fellow, Geoffrey Donnan.

It is most impressive to see how this embryonic unit has grown to 50 members. Also impressive is the depth and quality of the team. It is also broad geographically with the collaborating centres at the Royal Melbourne Hospital, the John Hunter Hospital in Newcastle and the Royal Perth Hospital. Even more impressive is the breadth in terms of a spread of clinical expertise and of basic neuroscience applied to MRI and PET imaging in stroke, and especially basic studies of neuroprotection in animal models. The current state of all of these areas, as well as the outcomes of local and international clinical trials, was well reviewed.

Heterogeneity appeared in the discussion many times. Not only the heterogeneity of stroke syndromes, but of the likely pathophysiology of lesions over time, over the spatial extent of damaged and threatened tissue, and of white matter versus grey matter.

Perhaps this heterogeneity makes it less surprising that no single agent neuroprotective clinical trials have succeeded. Future trials might be more successful if they employ combinations of agents, or physical interventions, designed to combat several points in the pathophysiological cascade of neural injury and death.

The promising results of neuroprotective agents, of many modalities of action, in rodent models stands in stark contrast to their failure in human clinical trials. David Howells interpreted this as evidence that the rodent models were inappropriate and that we therefore need models in a mammal whose brain more closely resembles the human in size, neuroanatomy and neurochemistry. The pig is one such mammal. At this time, there seems to be a compelling argument to evaluate neuroprotective agents in such a species before embarking on further large clinical trials.

Continued over…….
Emerging from both MRI and PET studies of the infarct core and penumbra, and their evolution over time, is the suggestion that small neuroprotective trials using these surrogate measures as proof of concept should precede large trials. It is conceivable that agents that demonstrate benefit in these surrogate measures might fail to show beneficial functional outcomes in large trials; however the converse seems quite unlikely – that agents inactive in a surrogate trial would later prove to be clinically efficacious. The surrogate trial might therefore serve as a screening test to reduce the chance of very expensive failure in formal large trials.

Disappointment with the neuroprotective trials and impatience to make progress, prompted the suggestion that we should “jump in and get on with” trials of multiple putative neuroprotective agents simultaneously, probably administered in the ambulance, before thrombolysis in the specialist centre.

Perhaps it is wiser to pause for a moment and await the outcome of imaging and functional studies with the pig model. In addition, we need to seek more information on the evolution of neurochemical changes in human stroke, perhaps with higher resolution MR spectroscopy. The spectroscopy study cannot provide the necessary sensitivity to answer all the questions we need to answer, but may provide markers that can be compared with more invasive techniques, such as microdialysis in animals. In any event, it seems wise to use focussed surrogate trials to test neuroprotective candidates before embarking on large trials with clinical outcomes.

It seems likely that future trials may test combinations of agents, rather than follow the tradition of single new agents alone. The combinations might include agents previously discarded after failure of efficacy as single agents.

The search for effective anti-hypertensive agents took decades and the critical role of the renin angiotensin system was not recognised early. The search for neuroprotective agents is more recent and, so far, the results have been rather bleak. Blood pressure is much easier to measure than neuroprotective efficacy, but it is end organ damage that is the clinically relevant end point in hypertension and this required outcome trials in animals and man. It may be that our understanding of the pathophysiology of ischaemic damage to the human brain lacks some critical component, identification of which will provide a dramatic breakthrough in neuroprotection. Alternatively, and perhaps more likely, progress will come in small steps and like childhood leukaemia and adult lymphoma, dramatic results will be the end result of combinations of small advances.
POST-RETREAT REPORT FROM DIRECTOR PROFESSOR G.A. DONNAN

Our first retreat was even more successful than we had anticipated. With about 50 people in attendance the presentations were of extremely high quality and the discussions always robust. We had hoped to focus less on review and more on future directions and I think we were successful in this endeavour. For any organisation it is very important to take stock and see where we have been as well as plan ahead.

Professor Fred Mendelsohn was an ideal facilitator. His breadth of knowledge from basic science through to the clinical sphere meant that he could focus the presenters and discussants on the important issues before us without being sidetracked into minutiae. Particularly I thought the discussion on where we should go with clinical trials while obtaining input from the basic science group including David Howells, Bevyn Jarrott and John Williams from the MR perspective was quite stimulating. The general view that we should plan combination neuroprotection trials seemed to be universal.

The success of the event suggests that we should repeat the process quite regularly. Brian Chambers and his team did an outstanding job in the difficult issue of organising the venue, obtaining sponsorship and making sure all the small details were taken care of. I thank our sponsors who were all well represented at the meeting and formed an important part of the increasing interchange between academia and industry. Most importantly I thank all the participants who helped make the event be so productive.

GEOFFREY A. DONNAN
POST-RETREAT REPORT – DR. KARIN SITTE

The inaugural stroke research retreat covered the complete range of research initiatives of the National Stroke Research Institute (NSRI) and its collaborating centres at the Royal Melbourne Hospital, John Hunter Hospital (Newcastle) and the Royal Perth Hospital. Past and present research of each of the NSRI divisions was presented. The aim of this summary is to capture the lively discussions that followed each presentation for the purpose of further developing research strategies and future directions. Reference to the abstracts are included in brackets to aid the reader.

Animal Models and Neuroprotectants

David Howells presented an overview of the current stroke animal models and their relative advantages/disadvantages (p15). The discussion focused on why most neuroprotectants have failed in human clinical trials even though they were successful in animal models. Failure of translation has not been the case for other rat models of disease. The following issues were identified as significant contributors to the failure of translational research in stroke:

- Rodents may not be the ideal animal model and a better model such as the dwarf pig model needs to be developed.
- Heterogeneity of stroke may have contributed to clinical trial failure.
- Permeability properties of neuroprotectants may differ in small rat brains compared to larger human brains.
- Successful therapy may need combinations of neuroprotectants and other drugs.
- Ischemic death process is multifactorial.
- In animal models the stroke is induced artificially and the exact time of stroke is known, this is not the case with humans where diagnosis occurs in a hospital setting hours later.

Following on the theme of neuroprotection strategies, Bevyn Jarrott explored the subject of novel neuroprotective agents particularly approved drugs (p16). Epogen and Minocyline are both approved drugs that have neuroprotective effects. The use of such drugs for neuroprotection would fast track effective therapies. The discussion raised questions on the proportion of apoptosis vs. necrosis as the underlying mechanism of cell death. The possibility of combined therapy with Minocyclin and Epogen was suggested. This issue of combined therapies was discussed in more detail in the Clinical Trials presentations.

Brain injury following stroke affects both grey matter and white matter, however the intracellular events leading to cell death in these tissues are very different. White matter seems to be more resistant to ischemia than grey matter. Geoff Donnan presented the case for distinguishing between neuroprotective strategies for grey matter and white matter (p18). Assessment of neuroprotectants in compartmentalised manner (grey matter vs. white matter) was discussed. In order to follow this approach, a relevant model is required. Suitable white matter model tissues include spinal cord and optic nerve, provided a “stroke model” can be developed with these tissues. Neuroprotectants are not tissue specific in the sense that they will act on the whole cell which is
composed of both grey and white matter. The processes of cell death in white matter are poorly understood. Is the process apoptotic or necrotic? This question may be answered using MR spectroscopy.

Anna-Maria Arabia presented the current status on stem cell technologies and how it could be applied to stroke as a cell replacement strategy (p16). There is evidence that stem cells injected intravenously will migrate to infarcted tissue. In addition, differentiated stem cells will integrate into neural circuits and remain viable for at least 3 months after injection. There is also evidence of endogenous activation of stem cells in injured brain tissue but it is not clear why these cells do not provide full compensation for the deficit resulting from the injury. Could there be toxic effects that inhibit the regeneration process? Mechanistic studies will be required to answer these questions.

Neuroimaging and Other Surrogate Markers

Ken Butcher introduced the subject of MRI techniques by comparing current and emerging MRI techniques to CT scanning as surrogate markers following stroke (p17). CT is used routinely and has very short acquisition times. In contrast, has longer acquisition times and gives more detailed information on perfusion changes and other cellular changes due to cytotoxic effects. MRI has great potential, particularly with the development of phosphorous imaging to detect metabolic changes and calcium imaging which may help in establishing the time at which the stroke occurred.

Stephen Davis expanded the theme of surrogate markers with particular reference to applications for clinical trials (p18). The discussion was centred on the argument of the validity of MR markers as surrogate markers. A clinical trial using MR markers is required to validate the technique. Surrogate MR markers should include a whole range of techniques detecting early changes such as the extent of the ischemic penumbra to BOLD as a measure of functional outcome.

A series of presentations followed with details on specific surrogate markers and how they could help in understanding the natural history of cerebral infarction and its parallels to animal models.

Thanh Phan, discussed F-MISO uptake as a measure of the extent of the penumbra in comparison to perfusion measures (p19). Geoff Donnan introduced physiological variables such as glucose concentrations as surrogate markers. How this could be applied was discussed in detail (p19). The main concerns were quantitation and the need to understand how these parameters change over time in relation to infarct evolution. David Reutens presented the idea of a probabilistic grey and white matter atlas to assess how these two tissues are affected by an infarct (p20). Questions on applications of this model were raised: Could this be used to understand the evolution of the penumbra? Could this model be used to evaluate the response to therapy?

Clinical Outcome Measures

The use of fMRI as a measure of functional recovery after stroke was addressed by Amy Brodtmann. This study used BOLD activation patterns as a measure of visual processing after stroke (p21). The effect of rehabilitation on this measure and the effect of aging were of great interest and may need to be investigated in more detail.
Julie Bernhardt discussed rehabilitation interventions in the management of stroke (p25). This is a complex topic that resulted in a lengthy discussion on experimental design. The main issues were the timing of rehabilitation and the varying standards of care across participating hospital. Should the study take into consideration standard of care vs late or early rehabilitation? Should the results of animal models where rehabilitation is forced rather than voluntary be taken into account?

The Future of Ultrasound
Chris Levi and Brian Chambers discussed progress in the area of emboli detection by ultrasound (p23). Ultrasound is a good surrogate tool for the detection emboli but its clinical utility is limited because it is very labour intensive. The technology is at a crossroad between an experimental tool and a clinical tool. Technological improvements are required to make the transition.

Clinical Trials
Geoff Donnan and Stephen Davis made joint presentations (p25) followed by a lively discussion where the following issues were raised:

- How should clinical trials be defined? Good quality studies looking at physical intervention beyond drug trial are essential.

- A ‘best treatment’ approach including neuroprotectant therapy either in the ambulance or within 3 hours preferably in direct comparison with tPA.

- Administration of neuroprotectants in combination, targeting different parts of the cascade. This would require pre-clinical studies in a relevant models such as the dwarf pig to ensure there is no unfavourable interaction between drugs.

- Focus should be on translational trials that build on existing strengths, namely good collaborations and innovation.

Epidemiology and Public Health
Mandy Thrift presented an update on NEMESIS and the potential for NEMESIS 2 was explored (p26). A second study would improve on the first if blood samples were to be collected for genetic studies, staffing levels were increased and neuroepidemiology were introduced in a collaborative fashion. It is predicted that the incidence of stroke may not decrease, but better treatment strategies may reduce mortality.

Lucinda Bilney described the outcomes of the National Stroke Units Program (p27). The conclusions from this study were treatment in a stroke unit reduces mortality by 20% but only 23% of patients get access to a stroke unit within a hospital. Quality practices are now recommending the setup of stroke units despite the fact that it is not a requirement. A hub-and-spokes model has been proposed where a central hospital forms the ‘hub’ and peripheral hospitals are the ‘spokes’. The challenge is to develop a model where the spokes are connected to the hub intellectually.
On a lighter note…memorable quotes:

“There are 11 slides but with the title slide there are only 10” – Stephen Davis

“It depends on the computer you use, Geoff gave me a very old computer” – Thanh on the amount of time it
takes to do automated analysis of DWI images

“Happy father’s day for those of you who are fathers and those of you who will be...” – Geoff’s introduction to
proceedings on Sunday morning.

“The fact that I have a trial called AVERT as an acronym, means I have been around Geoff Donnan for too
long” – Julie Bernhardt

“Let’s go the whole hog” – Geoff in relation to combination trials

“Call it the NIKE trial – just do it”– Bevyn on Geoff’s ideas
FRIDAY 30TH AUGUST

7:00pm  WELCOME DRINKS

8:00pm  DINNER

SATURDAY 31ST AUGUST

7:00am  BREAKFAST

SCIENTIFIC SESSIONS

8:20am  G. DONNAN  WELCOME AND OVERVIEW

Professor Donnan welcomed the participants, outlined the reason for the Retreat etc

8:30am  D. HOWELLS  ANIMAL MODELS FOR STROKE

Background: While thrombolysis has successfully reduced some of the burden of stroke, there has been a puzzling and frustrating inability to translate the clear experimental evidence for neuroprotection in rodents into clinical practice. For example, at least 15 NMDA receptor modulators have failed as have trials of different growth factors, Na/K channel blockers, neutrophil inhibitory factors, Ca^{2+} channel blockers and others. Importantly these failed trials have cost at least US$2 billion. A range of explanations have been put forward to explain these failures (Stroke 1999;30:2752-2758.). These include inappropriate extrapolation of the therapeutic time window from animal to human studies, failure to take into account white matter damage, differences in human and the models susceptibility to ischemia and neuroprotective agents, differential drug penetration to the target cells, adverse side effects of the neuroprotective agents and greater heterogeneity which may have masked beneficial changes which would have been apparent with better patient selection.

A more parsimonious explanation might be that our initial animal evaluations are inadequate.

Techniques: Techniques currently used to produce ischaemia in the middle cerebral artery vascular territory include direct surgical cautery or clipping of the MCA after craniectomy, introduction of fibrin rich emboli into the MCA, the injection of the vasoconstrictor peptide endothelin (ET-1 and ET-3) into the parenchyma adjacent to the MCA and occlusion of the MCA by the introduction of a “thread” into the internal carotid artery (ICA) to block the junction of the MCA and the anterior cerebral artery (ACA). Thread occlusion is perhaps the most widely used technique because it causes less direct cerebral trauma than direct microsurgical occlusion or injection of endothelin into the brain parenchyma, the lesions are more easily standardised than those produced by emboli, and the model lends its self to the study of reperfusion, a feature common to most human stroke.

No neuroprotectant has been systematically studied with these models in the face of co-morbidity caused by hypertension or diabetes, the risk factors most frequently associated with human stroke. An additional problem is that the small unfolded rodent cortex with blood supplied almost exclusively by the MCA does not mimic our large highly folded brains with different vascular territories supplied by distinct cortical arteries. The lack of folding and much smaller proportion of white matter also means that it is particularly difficult to evaluate white matter injury in rodent brains, an important issue since most neuroprotective strategies have concentrated on protection of neural cell bodies. Moreover, the stains for mitochondrial viability most often used to assess reduction of infarct volume and thus “neuroprotection” in animals have no direct counterpart that can be used to assess infarct or penumbral size after stroke in humans.

Outcomes: Clearly new approaches to the problem of neuroprotection in ischaemic stroke need to be taken. As part of this we propose a three tiered approach. Initially, thread occlusion of the MCA in rats will be used to screen potential neuroprotectants for activity. Promising compounds will then be studied in more detail using thread occlusion, endothelin and embolic models of stroke in rats with hypertension and diabetes before going on to evaluation in our dwarf pig model of stroke. These animals offer the advantage of a relatively large highly folded brain perfused by distinct cerebral arteries in which we can not only perform classical histological evaluation of infarct volumes, but can also use (and develop) equivalents of human MRI and PET surrogate end points to study the evolution of the infarct and penumbra in both grey and white matter.
Implications: Models that will predict success of translation of animal studies to man.

8:50am  B. JARROTT  NEW PHARMACOLOGICAL APPROACHES TO CEREBRAL ISCHAEMIA – CAN EPOGEN AND/OR MINOCYCLINE OFFER A FAST TRACK TO SAFE, EFFECTIVE NEUROPROTECTIVE THERAPIES?

Background: To date, no drug has been proven to be an effective neuroprotective drug against cerebral ischaemia despite hundreds of million dollars being expended in this area. Even if an effective drug was discovered in animal models of cerebral ischaemia tomorrow, it could be 5 years before this drug could be generally available even if no problems emerged in its clinical development. On the other hand, development would be speeded up if an existing, approved drug was found to be neuroprotective. EpoGen and Minocycline are two approved drugs that have been found to have very interesting neuroprotective properties in animal models of cerebral ischaemia.

Techniques: EpoGen and minocycline have been tested in rodent models of focal cerebral ischaemia and also contusive spinal cord injury and even when administered 3 hours after the ischaemic event, are markedly neuroprotective.

Outcomes: Both EpoGen and Minocycline are available as parenteral preparations and are reasonably safe drugs in humans. A Human Ethics Committee may be prepared to sanction ‘off-the label’ use of both these drugs for the treatment of cerebral ischaemia.

Implications: EpoGen is attractive for prophylactic use in patients at risk of stroke and is relatively safe provided the haematocrit is carefully monitored. Because it is a protein, it cannot be given orally – only sc or iv. However, the improved recombinant analogue, Darbepoetin alfa (Aranesp) has a much longer half life than EpoGen and a single, weekly injection may be sufficient for neuroprotection. Rodent studies also suggest that EpoGen could be effective in subarachnoid haemorrhage. It would not be justified to use Minocycline prophylactically as it is an antibiotic but it could be used acutely to treat cerebral ischaemia and contusive spinal cord injury.

9:10am  A. ARABIA  STEM CELLS: HOW CAN WE USE THEM IN STROKE?

It is now clear that rodents and mammals, including humans, exhibit neurogenesis in at least a limited number of brain regions, including the dentate gyrus of the hippocampus and the subventricular zone. The recent acceptance of the importance of neurogenesis can be attributed to several methodological developments such as new imaging techniques, confocal microscopy, more specific antibodies and sophisticated quantitative techniques such as stereology. In addition advances in stem cell research, particularly the ability to harvest both bone marrow-derived and neural stem cells has changed the way we think about the intact and injured brain.

It has been demonstrated that intravenous infusion of bone marrow-derived stromal cells in a model of stroke in rats gives rise to cells which express neuronal markers and improves functional outcome. Also, rodent fetal and adult neural stem cells, as well as human fetal stem cells, can be implanted back into the adult brain where they survive and differentiate into cells appropriate to the area of the brain to which they migrate. Interestingly, endogenous adult neural stem cells have been shown to differentiate into neurons following targeted apoptosis of cortico-thalamic projections, indicating that the brain has a dormant capacity for self-repair. If this is the case, appropriate stimulation could recruit native stem cells to enter a program of neurogenesis.

While the exact mechanisms by which exogenous or endogenous stem cells benefit the injured brain is not understood the pieces of the jigsaw puzzle are coming together to give us good reason to be excited about the use of stem cells in the treatment of neurodegenerative diseases and the injured CNS.

9:30am  J. WILLIAMS  MRI IN ANIMAL MODELS – CURRENT STATUS

Background: In vivo nuclear magnetic resonance spectroscopy experiments in physiological research have been increasing in popularity since the late 1970’s. The variety of sequence implementations and imaging modalities has increased significantly since these early time, with MRI now considered more that “just a tool to take pretty pictures”!

Some of the MR experimental modalities of current interest and application to Neurology, and more
specifically, to Stroke Research are:
- MRA & perfusion imagine (stroke)
- DTI & fibre tracking
- fMRI
- CSI
- Susceptibility-Weighted Imaging
- Spectroscopy

Unique qualities of NMR Experiments are:
- non-invasiveness
- allows repetitive measures
- can easily be combined with other measurement techniques.

Techniques: A wide variety of NMR techniques will be discussed, ranging from simple one-pulse to more complex diffusion tensor experiments.

Outcomes: Spectral quantification of tissue metabolites, surrogate markers of cellular and tissue damage, CBF characterization, etc..

Implications: NMR experiments offer a useful, non-invasive tool for temporal analysis of changes within target tissues following pathophysiological intervention. The power of comparing the results of injury within each animal (compared to a group of animals) allows much better characterisation of the timeline of processes involved. This is highlighted in treatment studies, where salvage of compromised tissue can be determined using a combination of imaging modalities.

9:50am  K. BUTCHER  MRI IN THE ASSESSMENT AND TREATMENT OF ACUTE ISCHAEMIC STROKE (RMH COLLABORATING CENTRE)

Background: The primary role of magnetic resonance imaging (MRI) in acute stroke is the identification of tissue that is potentially amenable to salvage with reperfusion and/or neuroprotective strategies. To date, the only effective acute stroke therapy is thrombolysis. This treatment is limited to a small portion of the stroke population by a restrictive time to treatment window (three hours) and the possibility of hemorrhagic transformation. The central theme of our work is that MRI parameters can be used to identify more rational selection criteria for thrombolysis. In addition, we hope to establish predictors of hemorrhagic complications of thrombolysis.

Techniques: Echoplanar MRI scans are performed in patients presenting with acute ischemic stroke symptoms. Diffusion weighed MRI (DWI) identifies the ischemic core in acute infarction, which exhibits restriction of water diffusion. Perfusion weighted MRI (PWI) demonstrates decreased regional blood flow. PWI are obtained by tracking the movement of a non-diffusible paramagnetic contrast agent through the cerebral circulation. Quantitative PWI measures, including mean transit time (MTT), regional cerebral blood flow (CBF) and blood volume (CBV), are calculated according to the central volume theorem.

Completed experiments include serial DWI and PWI studies of patients with acute ischemic stroke treated conservatively and in an open label fashion with the thrombolytic agent tissue plasminogen activator (tPA). A double-blind randomised trial of tPA versus placebo in acute stroke patients studied with DWI and PWI is ongoing.

Outcomes: In all studies DWI, PWI and final infarct volume as defined by T2 weighted MRI are used as surrogate outcome measures. Acutely, most patients present with a PWI abnormality that is larger than the region of DWI restriction. The region of mis-match between DWI and PWI abnormalities is defined as the penumbra. PWI abnormalities qualitatively predict cerebral infarction with high sensitivity. The final extent of infarction is quite variable; in most cases it is intermediate between the acute PWI and DWI abnormalities. Retrospective analysis indicates that treatment with tPA limits the expansion of the ischemic core (DWI lesion) as well as final infarct volume. Thrombolysis also increases salvage, or recovery, of the penumbral region. In addition, the likelihood of tissue infarction and salvage has been shown to be dependent on the degree of hypoperfusion, as defined by quantitative PWI, and the duration of decreased blood flow.

The Echoplanar Imaging Thrombolysis Evaluation Trial (EPITHET) is actively recruiting patients at this time. We hypothesize that in patients with a penumbral pattern, treatment with tPA between three and six hours after symptom onset will limit infarct core expansion. We also predict that hemorrhagic
transformation will be more likely in patients without a penumbral pattern, i.e. DWI lesions that are as large as acute PWI abnormalities at the time of treatment with tPA.

**Implications:** The characterisation of acute ischemic infarction with DWI and PWI is the most promising method for extending thrombolysis beyond the current three-hour time window. Ultimately, the use of MRI in acute stroke evaluation may therefore allow active treatment of a larger stroke population.

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**10:10am  G. DONNAN  WHITE MATTER ISCHAEMIA: WHAT WE KNOW AND WHAT IT MEANS**

**Background:** Most neuroprotective strategies are based on well known neurochemical cascades developed in animal models of focal cerebral ischaemia involving grey matter. The main feature of this cascade is neurotoxicity associated with excessive glutamate release and activation of glutamate receptors including NMDA and AMPA subtypes. However, we have now learnt that the glutamate mediated component of the cascade is fairly short-lived, probably in the first hour or so after onset of ischaemia and may be quite different in character to cascade of ischaemic events in white matter.

The proportion of brain made up of white matter in humans is approximately 50%. White matter is predominantly a compartment of connections either between grey matter compartments or between grey matter and spinal cord. The structure of white matter consists predominantly of axons, their surrounding myelin sheaths, oligodendrocytes and glial cells.

We now know that white matter appears to be more resistant to ischaemia than grey matter and has a somewhat different neurochemical cascade. Here, the initial ischaemic episode results in the release of adenosine as well as GABA from intrinsic stores. Adenosine and GABA receptors are then activated. Following this G protein kinase C cascade occurs with a feedback effect mediated by unknown mechanisms on the sodium-calcium exchanger, and ion channels. This results in a form of “auto-protection”.

Given that the majority of experiments using focal ischaemia for development of neuroprotective agents are performed in rats, and that the proportion of white matter in rats is probably only about 10%, there is a real need to:

1. Test neuroprotectants in larger animal models where there is a more equal distribution of white and grey matter;
2. Use a compartmental approach to neuroprotection in white and grey matter. Grey matter alone may no longer be an adequate pre-clinical benchmark.

**Techniques:** MR neuroimaging in animal models in humans to compartmentalise responses to therapy in grey and white matter. Similar techniques with 18FMISO PET in humans and 3HFMISO in animal models.

**Outcomes:** Response to therapies in grey and white matter compartments of brain in humans and animal models.

**Implications:** A compartmental approach to surrogate imaging outcomes may increase our understanding of the mechanism of action in vivo of a variety of neuroprotective agents. Agents which are effective in one compartment only are less likely to be clinically effective.

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**10:30am  MORNING TEA**

**SCIENTIFIC SESSIONS**

**11:00am  K. BUTCHER  MR COMPLETED (RMH COLLABORATING CENTRE)**

Abstract as first presentation at 9:50am.

**11:20am  S. DAVIS  MR FUTURE DIRECTIONS (RMH COLLABORATING CENTRE)**

**Background:** Echoplanar diffusion, perfusion and spectroscopic MR techniques allow the testing of new therapeutic approaches for stroke, with sample sizes of approximately 100 patients. These surrogate endpoints are now clinically validated and the studies can be performed in many tertiary centres in Australia. Current research protocols include the EPITHET trial, testing the hypothesis that treatment
responders to tPA can be selected beyond the clinically proven 3 hour time window and the GRACE trial, testing the hypothesis that intravenous insulin will produce better acute glycemic control in acute stroke and improve outcomes. Future approaches will include physiological modification (hypothermia) and combinations of thrombolysis with reperfusion (TWIN study), which can be first tested in proof-of-concept studies.

**Techniques:** Echoplanar magnetic resonance imaging of diffusion (DWI), perfusion (PWI) and spectroscopy (MRS) with quantitative measures of lesion volumes and chemical signatures including lesion lactate and NAA. Correlations with clinical measures of stroke severity including the National Institutes of Health Stroke Scale (NIHSS), Barthel Index (BI) and Modified Rankin Scale (mRS). Scan sequences usually involve pre-treatment, subacute post-treatment (usually 3-5 days) and outcome (30-90 days) protocols.

**Outcomes:** Attenuation of infarct growth using serial DWI measures, reperfusion, penumbral salvage, lesion lactate and NAA peaks. Correlation with clinical measures of stroke recovery and functional outcome.

**Implications:** Potential for translational research based on the animal stroke program at HFI and evaluation of other novel therapeutic strategies for acute stroke. Positive results would predict a higher likelihood of successful phase III clinical trials.

11:40am  T. PHAN  NEUROIMAGING STUDIES AT A&RMC

**Background & Techniques:** DWI provides an examination of the molecular motion of water. Within minutes of onset of ischemia, there is failure of ATPase pump and restricted motion of water. This is manifested as bright signal on DWI images and low values on apparent diffusion coefficient (ADC) of water map. Previous studies on DWI have been concentrated on volumetric correlation with the final infarct volume. However, recent reports with rt-PA suggest that the fate of tissue with DWI abnormality is not predetermined. Here, we have examined patients who had MR imaging and PET imaging with FMISO ligand. FMISO ligand is trapped by hypoxic tissue but not by normal tissue. Tissue binding of FMISO was determined using statistical parametric map. DWI abnormality was determined by the presence of bright signal on DWI and low ADC values. Using voxel by voxel comparison, we have found binding of FMISO in regions of DWI abnormality. There are several possible explanations for this phenomenon: (1) energy failure is not complete within DWI lesion; (2) the threshold for trapping of FMISO may be lower than for ATPase pump.

Perfusion MR imaging (PI) has attracted a lot of attention particularly with online analysis of DWI and PWI mismatch soon becoming a reality. However, there are several concerns with PI. These include determining which perfusion maps to use (mean transit time map (MTT), time to peak map (TTP), relative cerebral blood flow (rCBF) map and relative cerebral blood volume (rCBV) map). We have explored the relationship between relative cerebral blood flow and the risk of infarction on a voxel by voxel basis. The rCBF map was produced by dividing the integration of the time contrast curve by time.

Automated detection and volumetry of acute ischemic stroke has assumed great clinical and research significance with the drive towards treatment of ischemic stroke guided by diffusion and perfusion MR studies. Manual measurement of infarct volume on DWI is difficult and time consuming. Ischemic tissue is defined by the presence of high signal intensity on DWI and low values on apparent diffusion coefficient (ADC) maps. An automated algorithm allows consistent ischemic tissue volume measurement without the bias introduced by different observers. This algorithm process medium and large size MCA territory infarct well.

**Outcomes & Implications:**
1-Not all DWI abnormality in the hyperacute phase of ischemic stroke are destined for infarction
2-The risk of infarction rise dramatically as rCBF dropped below 70% of the contralateral side.
3-Our algorithm for detection and volume measurement of acute ischemic stroke on DWI is reliable, fully automated and requires no user interaction.

12:00pm  G. DONNAN  MR FUTURE DIRECTIONS (NSRI)

**Background:** There are a number of ongoing and planned projects involving MR at NSRI. These are best summarised as follows:

1. **White matter:**
i. Since the penumbral distribution and behaviour in white vs grey matter may be quite different this has been demonstrated using the FMISO technique in humans, this will now be also tested using MR DWI/PWI mismatch techniques in a population of patients with acute ischaemic stroke (n approximately 70).

ii. Validation of “penumbragram”. The temporal and spatial resolution of the ischaemic penumbra has been statistically quantitated using the “penumbragram” technique with FMISO PET. This will also be validated using MR DWI/PWI approaches.

iii. Since the animal models of neuroprotection have mainly been grey matter based, it is important to understand the proportion of white vs grey matter affected by cerebral infarcts in patients undergoing neuroprotection trials. The distribution of infarct patterns in all neuroprotection trials at NSRI (n approximately 50) will be determined by overlay techniques on a probabilistic map of grey/white matter distribution.

2. Sample size for surrogate outcome studies using MR: Surrogate MR signatures are becoming increasingly useful in phase II proof of concept studies of therapy. However there is little understanding of the natural history of some of these outcome measures, particularly with relation to early time windows of initial infarct volume measurement (usually DWI) and growth to outcome measure (usually T2 at one month or 3 months). A collaborative study usually involving centres in Australia and North America is being undertaken to develop accurate sample size calculations based on surrogate outcomes of infarct growth and tissue salvage. Five centres are currently involved.

3. Influence of physiological variables on surrogate MR measures: The importance of physiological variables on surrogate outcome measures is beginning to be understood. The influence of glucose has become established but others including blood pressure and temperature are less well documented. Probably the most powerful influences on outcome measures is arterial patency and time of imaging. Together with physiological variables these will be entered into a multivariate model of MR outcomes such as infarct growth and tissue salvage.

4. Quantitation of MR CBF: While MTT and TTP are commonly used indices of perfusion on PWI MR maps, they are not currently quantifiable. Using the approach of multiple arterial input elements, a quantitative CBF map is being developed.

5. Probability map of MCA territory: The middle cerebral artery territory has become extremely important in trials of therapy, particularly thrombolytic agents. It seems likely that early ischaemic changes may be a predictor of poor outcome although this issue remains controversial. If an automated map of middle cerebral artery territory with true volume of territory could be established and proportion which has developed early ischaemic changes quantitated this may be clinically useful. Using the probabilistic approach, a map of middle cerebral artery territory will be generated in cases where occlusion of middle cerebral artery is documented on MRA and infarction of middle cerebral artery territory is found.

Techniques: MR DWI/PWI and T2 surrogate markers of outcomes.

Outcomes: Standard MR surrogate outcome measures such as infarct growth, tissue salvage together with the T2 probabilistic maps.

Implications: MR continues to be an important tool in surrogate outcome measures in phase II proof of concept trials. A better understanding of these issues is likely to reduce sample sizes of phase III clinical trials of therapy.
patients and a groups of normals. The methods take into account multiple comparisons, for which the Bonferroni correction would be prohibitively conservative. They also take into account dependence between nearby voxels by estimating resolution elements. The latter uses information from the variance-covariance matrix of the partial derivatives of the statistic image. This method of mapping was validated against a non-parametric method based on the bootstrap, which makes no distributional assumptions.

A method of comparing infarcts from different patients was then developed by mapping the volume of penumbra in regions of the infarct. The regions were defined with reference to the centre of gravity of the infarct and core, periphery and external regions were identified on infarcts manually segmented on the late CT scan. The behaviour of this method of data reduction was then examined by examining the correlations between defined penumbral volumes and time. A factor analytic approach was also taken where no a priori definition of infarct core was used. Instead, the factors correlating strongly with log time were examined and subregions with high weights were allocated to membership of the infarct core or periphery. The results of factor analysis agreed broadly with the regions defined a priori.

Outcomes and Implications: Using these techniques, we have observed persistence of penumbral tissue with temporal evolution in its spatial distribution from infarct core to periphery. An inhomogeneous spatial distribution within the vascular territory affected is also seen, presumably reflecting the pattern of collateral circulation. The distribution of tracer uptake in grey and white matter was also examined.

12:40pm  D. REUTENS  PET - FUTURE DIRECTIONS (NSRI)

Future directions in PET:

1. Validation of F-MISO against traditional measures of penumbra (CBF/CMRO$_2$)

   In these studies we plan to perform studies with [$^{11}$C]FMISO as well as CBF and CMRO$_2$. The aim of these studies is to FMISO uptake against penumbral thresholds defined with blood flow and oxygen consumption. One criticism of the FMISO method has been that it may include tissue which is hypoxic but for which viability is not under threat.

2. Can we obtain useful FMISO information using after shorter intervals

   In these studies we plan to determine whether useful FMISO uptake information can be obtained using short dynamic scans

3. Mapping of microglia using [$^{11}$C]PK11195

   [$^{11}$C]PK11195 binds to the peripheral benzodiazepine receptor which is present on microglia and on macrophages. These cells may be involved in post-stroke damage or repair. We plan to examine uptake of this tracer post stroke and to examine correlations with outcome.

4. Development of apoptotic markers

5. Labelling of potential neuroprotectants

1:00pm  LUNCH

7:30pm  DRINKS

8:00pm  DINNER

SUNDAY 1ST SEPTEMBER

7:30am  BREAKFAST

SCIENTIFIC SESSIONS

9:00am  A. BRODTMANN  HEMODYNAMIC RESPONSE TO FACES REMAINS STABLE UNTIL THE NINTH DECADE
Background: It has been suggested that fMRI activation in older subjects may not be as robust as that seen in younger subjects. Previous studies have examined the hemodynamic response (HDR) elicited by a visual chequerboard stimulus (1), as well as HDR variability in primary sensorimotor cortex (2). Most visual experiments have focused on calcarine cortex, rarely examining individuals over the age of 70 or as a function of chronological age. We examined the HDR and activated voxel number by decade in a group of healthy elderly participants in ventral extrastriate and striate cortex in response to viewing visual stimuli (face, scrambled faces) while detecting visual targets.

Techniques: Activation Task: A block design with 3 stimulus conditions (A: faces, B: scrambled faces, C: 50% grey field) alternating in ACBC sequence was used with a block duration of 20 seconds, and 3 cycles within the imaging run. A central black fixation cross was superimposed on all visual stimuli. Subjects monitored the display for transient changes in the fixation cross from black to white (target).

Data Acquisition: MR images were acquired on a 3T GE scanner. Fourteen coronal slices beginning at primary visual cortex were selected for gradient echoplanar imaging (EPI: TR=2000, TE=40, FOV=24, matrix 128x128, slice thickness=4 mm, gap=1 mm). Coronal T1 and MRA images corresponding to EPIs, as well as an axial 3D SPGR sequence (2 mm continuous slices, 512x512 matrix) were acquired on each subject.

Data Analysis: Following motion detection and correction (AIR algorithm), T-test maps were obtained for faces vs grey field, and for scrambled faces vs grey field and thresholded to p-value < 0.001 (uncorrected) in MEDx3.2. Regional HDRs were generated from thresholded activated voxels for each region (left and right ventral extrastriate cortex). Individual subject time courses were then grouped by decade for ventral extrastriate cortex (Figure 1). Identical analysis was performed on the left and right striate cortex (not shown).

Outcomes: Robust activation was observed for both faces and scrambled faces in all decades (Figure 1). Overall there were no differences in HDR shape, amplitude or latency as a function of decade. Average activated voxel number per condition reduced by 50-75% after the seventh decade, but then appeared to remain stable.

Implications: Functional neuroimaging in the elderly poses unique problems and more normative data is required before the interpretation of these tests can be done accurately in disease states. Extrastriate cortex activation for real images (eg faces, abstract images) is readily elicitable until the ninth decade.

9:20am  L. CAREY  MOTOR AND SENSORY ACTIVATION: PAST AND FUTURE

Background: Brain networks may reorganise to enhance stroke outcomes. However, little is known about the evolution of cerebral changes associated with post-stroke motor and somatosensory recovery nor the mechanisms underlying training-induced recovery post-stroke in humans. Investigation of the potential benefits of experience in facilitating brain reorganisation is essential to advance the development and testing of scientific-based therapies. Our aim is to serially investigate the relationship between loci of brain activation and motor or sensory recovery during the sub-acute period of recovery, ie 2 weeks to 7 months post-stroke, under both spontaneous (motor and sensory) and training-induced (sensory) conditions.

Techniques: Serial whole-brain activation images were obtained at 2-7 weeks, 3 months and/or 6 months post-stroke using positron emission tomography (PET) and/or functional magnetic resonance imaging (fMRI) during performance of a simple finger-tapping task or controlled touch stimulation of the fingertips. Quantitative measures of finger tapping ability and touch discrimination were developed and an index of recovery determined. Loci of activation were determined using statistical parametric mapping (SPM96, SPM99, iBrain) and compared within individuals, across groups and over time. Data was interpreted relative to individual and standardised brain maps.

Outcomes: Healthy controls: Reproducible loci of activation associated with motor and sensory paradigms were defined in older healthy controls at both group and individual levels. Motor studies (stroke): Activation of expected motor regions and recruitment of new sites occurred early post stroke. Good recovery was associated with additional SMA activity early, relative to controls, followed by return to a more normal pattern. Increased activation of contralateral SMI and bilateral SMA early was associated with good, rather than poor, motor recovery. Sensory studies (stroke): The potential for return of activation in brain regions normally involved in touch discrimination, ie. primary and secondary somatosensory cortices, has been demonstrated in individual stroke patients following both spontaneous and training-induced recovery.
**Implications**: Changes in loci of activation may be confidently monitored over extended time intervals (6 months) and interpreted relative to expected variation quantified in mature healthy controls using motor and sensory paradigms that are robust and biologically stable. Identification of neuroanatomical sites/systems involved in spontaneous and training-induced recovery post-stroke is important to guide development of scientific-based therapies and may have some predictive clinical significance. Our findings to data suggest that changes are dynamic, appear to be related to recovery and may be influenced by training even following extended intervals of poor spontaneous recovery. Further, good recovery was associated with recruitment within the pre-existing system and involved both primary and secondary motor and sensory areas.


**Dextran in Carotid Endarterectomy (DICE) Phase I**: **Aim**: To test the hypothesis by randomising patients undergoing CEA for atheromatous disease to receive either perioperative 10% dextran 40 or normal saline placebo and measuring microembolism in the ipsilateral middle cerebral artery using TCD. **Current Status of the Study**: The study has been completed and results have been published in a peer reviewed journal and have been presented at national and international conferences. A larger scale, NHMRC funded study is currently underway evaluating the effect of 10% dextran 40 on rates of stroke and death at 30 days postoperatively.

**Asymptomatic stenosis embolus detection (ASED) study**: **Microembolism as a risk factor for cerebral ischaemia in asymptomatic carotid stenosis**: **Specific Aim**: The specific aim is to test the hypothesis by performing serial transcranial Doppler embolus detection monitoring, carotid duplex ultrasonography and prospective clinical neurological assessment for patients with 60-99% asymptomatic carotid artery stenosis. **Current Status of the Study**: Recruitment into this study has now been completed and analysis of the data is currently underway. Over 200 patients were recruited into the study with 231 eligible arteries. These patients were followed for a mean of 27 months (range six to 61 months). 72 (31%) arteries had 80-99% stenosis. Two patients suffered strokes and further five had hemispheric TIAs, two had retinal infarcts and four had amaurosis fugax attributed to the study artery giving a 2.8% event rate per patient per year or a 2.5% event rate per artery per year. There were 14 other non-study artery cerebral vascular events (seven strokes, four TIAs and three retinal insults). 27 patients died including 12 from non-cerebral vascular disease.

**Visual Function after Coronary Artery Bypass Grafting**: **Hypotheses** - Visual Form and Motion (VFM) testing will be sensitive to cognitive impairment in patients post-CABG; and Microemboli detected in the intracranial vasculature during surgery by Transcranial Doppler will predict the severity of VFM impairment. **Current Status of the Study**: The study is ongoing and preliminary results from this study have been presented at a number of national and international conferences (please refer to attached presentation and publication details).

**The accuracy of intracranial large artery occlusive disease assessment using transcranial colour coded duplex sonography**: **Aim**: It is the aim of this study was to evaluate the accuracy of TCCS in the diagnosis of intracranial occlusive disease in patients referred for investigation of cerebral ischaemia, with MRA being used as the comparison imaging modality. **Current Status of Study**: The data collection for this project has been completed and preliminary results have been presented at a number of national and international. Data analyses are being carried out and a paper is being written for submission to a peer reviewed journal.

**The influence of acute carotid and transcranial colour coded duplex on the assessment of ischaemic stroke mechanism**: **Aims**: To evaluate the frequency with which use of the combined CD and TCCD within 24 hours of onset of cerebral ischaemia changed the initial clinical assessment of stroke mechanism to concur with the final assessment of stroke pathophysiology. **Current Status of Study**: The study is ongoing and preliminary results from this study have been presented at a number of national and international conferences.

**Assessment of cerebrovascular compliance in cognitively impaired patients**: **Hypotheses**: 1. That magnetic resonance (MR) and imaging measurements of cerebrovascular compliance will correlate with
clinically defined entities of cognitive impairment, vascular dementia and Alzheimer’s disease (ie. reduced in patients with vascular dementia and increased in patients with Alzheimer’s disease relative to a healthy elderly population). 2. That transcranial colour coded duplex (TCCD) measurements of venous pulsatility will correlate with MR measures of vascular compliance (ie. the middle cerebral vein pulsatility will be significantly higher in patients with vascular dementia in comparison to the other patient groups).

**Current Status of Study:** Recruitment into the study has commenced and it is anticipated that we will have collected sufficient pilot data to enable us to submit an application for an NHMRC Project Grant in 2003.

**Composition of Cerebral Microemboli Determined using Transcranial Doppler Monitoring during Coronary Angiography:**  
**Aim:** The aim of this study was to examine the occurrence of brain embolism during the various phases of CA, determine the likely composition of emboli detected during these phases using ES intensity criteria, and to determine how manipulation of catheters or wires may contribute to the shedding of emboli.  
**Current Status of the Study:** The study has been completed and results analysed and presented at an international conference.

**Normal blood flow velocities in the intracranial large arteries as measured by transcranial colour-coded duplex:**  
**Current Status of the Study:** The study is ongoing, however, preliminary results have been submitted for presentation at the upcoming Stroke Society of Australasia Annual Scientific Meeting.

**Implications:** Ultrasound techniques, particularly using emboli detection with Transcranial Doppler form useful surrogate endpoints for both trials of therapy and natural history of disease. Increased use of this approach may reduce the need for large phase III clinical trials or enable those being conducted to have a greater likelihood of success.

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**10:00am  B. CHAMBERS  ULTRASOUND: FUTURE DIRECTIONS (NSRI)**

**Background:** Ultrasound has important strengths alongside other imaging modalities especially portability, non-invasiveness, and suitability for monitoring. These strengths need to be exploited for future research.

**Techniques:** The most promising areas of research appear to be in the post-operative recovery room and emergency room settings.

Transcranial Doppler (TCD) monitoring for embolic signals (ES) after carotid endarterectomy (CEA) provides a useful surrogate for the outcome of TIA and stroke. Treatments which reduce ES probably reduce the incidence of clinical events although this has yet to be proven. Dextran has a weak effect on ES but potent antiplatelet agents such as glycoprotein IIb IIIa receptor antagonists should have a more powerful effect on ES.

TCD monitoring of patients with acute ischaemic stroke, particularly those with embolic occlusion of the middle cerebral artery, can help determine when recanalisation occurs. At present this is under-utilised yet it could prove a valuable adjunct to other investigations in patients undergoing thrombolysis. MRI/A, which is difficult to get done at all in acute stroke patients, can seldom be repeated. Moreover, there is some evidence from other centres that ultrasound energy focussed on an embolus during TCD monitoring actually enhances thrombolysis. This important observation needs to be confirmed.

**Outcomes:** Demonstrating that a certain agent reduces ES after CEA should be a pre-requisite for a clinical trial investigating the effect of the agent on clinical outcomes.

Monitoring recanalisation in patients receiving thrombolysis may lead to tailoring the dose and route of administration of tPA for a particular patient, and possibly to widening of the therapeutic window.

**Implications:**

1.) TCD monitoring for ES is labour-intensive and an automated system is necessary.

2.) There may be opportunities for pharmaceutical company funding.

3.) Each of the areas of future research will require a research fellow working specifically in that area.

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**10:20am  J. BERNHARDT  A VERY EARLY REHABILITATION TRIAL (AVERT)**
Background. Stroke is the leading cause of disability in Australia, accounting for 25% of all chronic disability. The development of treatments that are successful in reducing the costs of stroke, both individual and community, are vital. Recently, the authors of a longitudinal observational study found that very early (day 1) mobilisation after stroke was a strong predictor of reduced bed associated complications, faster recovery of walking and early return home. This preliminary finding needs to be tested rigorously. Hence, we plan to conduct the first multi-centre randomised controlled trial of very early rehabilitation after stroke.

Techniques. We hypothesise that early rehabilitation could reduce death and disability at 3 months. There will be three phases to the study. Phase 1: determine baseline levels of rehabilitation input at 5 metropolitan stroke units. Behavioural mapping, an observational technique was used to derive data for this Phase. Phase 2: a pilot will employ a randomised, single blind, controlled trial of intervention. Phase 3: the trial will be extended to multiple centres Australia wide.

Results from the 58 patients recruited to Phase 1 indicate that: overall, patients spend less than 12% of their day engaged in activity that promotes recovery of movement; patients spend 60% of the day alone, with family playing a supporting major role. Only 15% of patients were restricted to bed for medical reasons on one of both days of observation, the remaining 85% were medically stable. These results indicate significant scope for improvement in the interventions offered to patients in the acute phase after stroke.

In Phase 2 we expect to recruit 280 patients to the trial in the first year. Of these, half will be randomly allocated to early rehabilitation and half will receive standard care. Early rehabilitation subjects will have treatment twice a day, seven days a week for the first 14 days only. A research officer blinded to group will assess outcomes, these will be taken on admission, 14 days, 3, 6 and 12 months post stroke.

Outcomes. The primary outcome is the number of patients dead or disabled (Barthel < 20) at 3 months. Secondary outcomes will include post stroke complication rates, time to walking independent of physical assistance, total length of hospitalisation, discharge destination, quality of life and costs of care.

Implications. Significant changes to current clinical practices may result from this trial.

10:40 MORNING TEA

SCIENTIFIC SESSIONS

11:10am S. DAVIS CLINICAL TRIALS COMPLETED (RMH COLLABORATING CENTRE)

Background: Clinical trials in stroke have broadly included acute stroke trials and secondary prevention trials. Acute stroke trials have chiefly focused on thrombolytic therapies (eg Australian Streptokinase Trial - ASK, ECASS II) or neuroprotective strategies (eg NMDA antagonists, growth factors, anti-inflammatory approaches, free radical scavengers). Australian involvement has been chiefly in phase III trials, but the trend will be to earlier phase I/II trials. Physiological studies have included initial hypothermia work (COOLAID) and modification of the glycemic environment (GRACE). Multimodal approaches are anticipated, including neuroprotection and thrombolysis. Secondary prevention trials have involved antiplatelet approaches (CAPRIE, MATCH, ARCH), endarterectomy trials (NASCET), BP reduction (PROGRESS) and cholesterol lowering (SPARCL).

Techniques: Chiefly phase III clinical trials, but an increasing trend to phase I/II trials (eg EPITHET, GRACE). Considerable opportunity for local translational research.

Outcomes: Australia has developed an excellent international reputation for the performance of both acute stroke and secondary prevention trials, facilitated by the Australasian Stroke Trials Network. In acute stroke, only thrombolysis has been effective, using tPA, but the ASK trial put Australia on the international trials map. Acute antithrombotic strategies with heparin, low MW heparins and heparinoids have been ineffective in phase III trials, with exception of a very modest benefit shown with acute aspirin. All neuroprotective strategies have failed in phase III trials for a variety of reasons. Physiological approaches appear promising. In contrast, most secondary prevention trials have produced positive results, particularly with combination antiplatelet therapies and blood pressure lowering after acute stroke.

Implications: We are now poised to rapidly translate lab research strategies into the clinical arena. It is anticipated that there will be a shift from phase III to phase I/II trials.
**Background:** A number of issues will be addressed in the coming years. These include;

**New clinical trial structures:**

i. **Clinical Trials Victoria (CTV):** This new initiative involving partnership between the Alfred Baker Centre for Development of Cancer Therapeutics (CDCT), Neurosciences Victoria (NSV) and Melbourne Health has been developed with Strategic Technology Initiative (STI) funding. This will provide an important base for clinical trials in Victoria.

ii. **National Neuroscience Facility (NNF):** Here neuroscience trials Australia wide will be developed including the groupings of stroke, epilepsy, movement disorders, MS, dementia, neurosurgery and psychiatry. Again this will form an important base for ongoing commercial and investigator driven trials.

**Possible new trial directions:**

i. **Thrombolysis With Neuroprotection trial (TWIN):** Patients receiving tPA within 3 hours of ischaemic stroke will receive either tPA plus placebo or tPA plus neuroprotectant. The most obvious neuroprotectant to start with would be minocycline. This would be conducted as a phase II proof of principle trial with clinical outcome measures. The possibility of administration of the neuroprotectant in the ambulance or home will be explored.

ii. **Modification of physiological variables:** Ongoing studies of glucose modification in phase II trials (GRACE) are continuing. The possibility of developing blood pressure lowering trials or temperature modification will be discussed.

iii. **EPITHET II:** Lower tPA dose with longer time window could be considered.

iv. **Australian Urokinase Stroke Trial (AUST) or POsterior circulation Stroke Trial (POST):** Should these be reactivated?

v. **Australian Streptokinase Trial (ASK II):** Should this be reactivated with 3 hour time window and dose ranging elements?

vi. **Combination neuroprotection trials:** A combined approach of temperature lowering, best combination license neuroprotectants, glucose and blood pressure control could be considered given that this may have the greatest likelihood of a “black box” effect.

**Techniques:** Standard clinical trial techniques.

**Outcomes:** Combined death and disability for most trials as outcome measures but some phase II proof of concept studies may require MR surrogate outcomes to be used.

**Implications:** New clinical trial structures should allow more investigator driven trials to be conducted in Australia. The next phase of clinical trials will be focused on either new means of administration of thrombolysis with or without neuroprotectants. Modification of physiological variables will also be important.

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**Background:** Stroke is a major cause of mortality and morbidity with a high proportion of survivors being severely disabled. Despite the clear importance of stroke as a health problem, little is known about the long-term outcome of stroke patients in Australia and there has been very limited information about the financial costs of stroke to our society or to the sufferers and their families. To address these issues we have been conducting the North East Melbourne Stroke Incidence Study (NEMESIS). This is the major study currently being undertaken within this Division.

**Techniques:** This is an epidemiological study in which the ‘ideal’ criteria for stroke incidence studies have been utilised. Stroke patients have then been assessed at regular time intervals.

**Outcomes:**

- Accurate measure of the incidence of stroke, and its subtypes.
- Costs of stroke.
- Long-term (3-5 year) outcome of stroke particularly in relation to dementia, recurrent stroke, quality of life, dependency, and survival.
- Adequacy of management of risk factors among stroke patients, e.g. hypertension, atrial fibrillation, etc.
Implications:

Incidence, costs and risk factor assessment will allow adequate assessment of service provision, burden of stroke, and targeted prevention strategies. Future research leading from these findings are:

- Validation of causes of death with official statistics.
- Longer term follow up of patients in NEMESIS (to 10 years).
- More accurate estimates on stroke costs.
- Repeat incidence study to investigate changes in incidence over time.

Current and potential collaborations are:

- Victorian Cohort Study (ViCS)
- International Stroke Incidence Study Data Pooling Project
- International Stroke Outcomes Study
- Validation of Incidence Methodology (King's College London)

Background: Distinction needs to be drawn between the two roles of Public Health: Research which falls under the banner of NSRI and NSF’s policy and advocacy role which is informed by the research. The more effective and efficient delivery of stroke services has been the major focus of the work of the Public Health division.

Projects:

SCOPES (Stroke Care Outcomes: Providing Effective Services)

SCOPES II Study
National Stroke Unit Program
MORUCOS (Model of Resource Utilisation and Cost for Stroke)

Outcomes:

- Profile of stroke care in Victoria and comparative analysis of stroke care delivery models.
- Development of priority process indicators for acute stroke care.
- Patient outcomes to 6 months and two years after stroke.
- Prevalence and impact of sleep disordered breathing in stroke patients.
- Situational analysis of stroke delivery across Australia.
- Preliminary work on potential for innovative stroke care delivery models.
- A model which can be used to describe and predict resource use and costs of stroke and decide between different interventions.

Future: Vision 33 – reduce disability, handicap and mortality from stroke by 33% in 10 years. NSF to develop a plan to achieve this, informed by research of public health and other divisions as to gaps in evidence.

Potential areas of future work:

- Further use of MORUCOS to inform funding of different interventions for stroke.
- Marrying of data from SCOPES and SCOPES II to identify longer-term patient outcomes.
- Further economic analysis of SCOPES.
- Economic modelling of stroke models (other states, smaller hospitals, rural settings).
- Implementation of NSUP models of stroke care delivery.
- Possible further sleep disordered breathing study in a larger cohort.
NAME: DR ANNE L ABBOTT (NEE HARRIS)

Position: Research Fellow in Stoke Medicine

Institution: ARMC/NSRI

Contact details: Neurology Dept, Repat. Campus, ARMC, Locked Bag 1, Heidelberg West, Victoria, Australia, 3084. Phone 9496 2845: Fax 9496 4065

Qualifications: MBBS, FRACP

Research experience: Completing a Ph D

Current research interest: Stroke medicine

Relevant publications:


NAME: ANNA-MARIA ARABIA

Position: Research Officer

Institution: University of Melbourne, Department of Medicine

Contact details: 03-9496-3257; 0412-940-921, e-mail: aarabia@unimelb.edu.au

Qualifications: Doctor of Philosophy (Ph.D.) (July 1997 - December 2001)The University of Melbourne, Department of Pharmacology, Baker Medical Research Institute, Central Cardiovascular Control in Rats with Heart Failure. Bachelor of Science (Honours) (1992- 1996), University of Melbourne, Department of Medicine, Austin & Repatriation Medical Centre, Major Studies: Neuroscience and Pharmacology, Honours Thesis title: The Molecular Characterization and Pharmacology of Cerebral Infarction and Spreading Depression.


Current Research Interest: My current research investigates the aetiology of cerebral ischemia. I am particularly interested in understanding the role of both adult stem cells and the immune system in models of CNS injury. In addition, I wish to explore the possibility of using stem cells in the treatment of stroke in humans.
Relevant publications:


3. **M.D. De Simoni, M. Barba, C. Storini, L. Catapano, A.M. Arabia and L. Bergamaschini.** Neuroprotection by complement (c1) -inhibitor in mouse transient brain ischemia. (submitted)

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**NAME: TRACEY BAIRD**

**Position:** Research Fellow

**Institution:** Dept of Neurology, Royal Melbourne Hospital, Parkville, Vic 3050

**Contact details:** Email – tracey.baird@mh.org.au; Phone – 03 9342 7917

**Qualifications:** B.MSci (Hons) University of Dundee; MbCHb (Hons) University of Dundee; MRCP (Glas.UK)

**Research experience:** Current position as holder of SHERT Nasmyth scholarship, involved in acute stroke research at Royal Melbourne Hospital. Previous involvement as neurologist/clinician in stroke outcome research, at Institute of Neurological Sciences, Southern General Hospital, Glasgow.

**Current research interest:** The influence of diabetes in stroke outcome; Imaging of acute stroke; Acute stroke thrombolysis.

**Relevant publications:**


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**NAME: PETER BATECHLOR**

**Institution:** Austin & Repatriation Medical Centre

**Qualifications:** FRACP, PhD, MBBS, BMedSci

**Research experience:** 2001: Awarded Early Career Researcher Grant by Melbourne University; 1997-2000 PhD. TOPIC: Cellular and molecular mechanisms of axonal sprouting in the injured CNS, University of Melbourne, SUPERVISORS: Dr David Howells (Department of Medicine, University of Melbourne) and Professor Geoffery Donnan (Department of Neurology, A&RMC); 1999 Winner Istvan Tork Student Oral Prize for best student oral presentation at 1999 Australian Neuroscience meeting; 1997 Awarded NHMRC Medical Postgraduate Research Scholarship; 1997 Awarded Gustav Nossal Medical Postgraduate Research Scholarship for the NHMRC proposal with the most merit; 1987 B.Med.Sci. (first class honors). TOPIC: Nerve growth factor receptor and choline acetyltransferase co-localisation within the rat forebrain: collateral sprouting in response to fimbria-fornix transection, University of California San Diego, SUPERVISORS: Professor Fred Gage (U.C.S.D.) and Dr David Ehrlich (Monash Dept. Anatomy).
Relevant publications:

2. Batchelor PE, Porritt MJ, Parish CL, Martinello P, Liberatore GT, Donnan GA and Howells DW Macrophages and microglia produce local trophic gradients that may stimulate axonal sprouting towards but not beyond the wound edge. MCN In press (2002).

NAME: DR JULIE BERNHARDT

Position: Post Doctoral Research Fellow

Institute: National Stroke Research Institute

Contact: Ph 03 9496 2783 Fax 03 9496 2650, JBernhardt@austin.unimelb.edu.au

Qualifications: BSc (Physiotherapy) 1985, Lincoln Institute of Health Sciences, Melbourne, Grad Dip Research Methods 1992, La Trobe University, Melbourne, Ph.D 1998, La Trobe University, Melbourne

Research experience: In 1990 I started work in rehabilitation at Mount Royal Hospital. This provided a rich clinical research environment. Primarily my colleagues and I were interested in improving knowledge about stroke rehabilitation practices, including how well therapists could predict outcome, whether upper limb treatments could be made more effective, and learning about patterns of recovery of balance after stroke. These projects culminated in several publications. More importantly, they promoted further questioning of current practices, prompting all of us to enrol in research degrees. Since 1995 I have combined a clinical position with my PhD research and a role as Physiotherapy Research Coordinator at Broadmeadows Heath Service, then North West Hospital and now Melbourne Extended Care & Rehabilitation Service. In this role I promote evidence based practice, and support projects such as an RCT of shoulder strapping to prevent hemiplegic shoulder pain, the use of Uptimers to study activity levels after hip fracture in the frail elderly and a number of projects studying falls and balance after stroke. I submitted my PhD in 1998. My research focussed on upper limb recovery after stroke and the role of experience and training in the accurate assessment of movement disorders. In 1998/99 I worked with Leeanne Carey at the NSRI, and at North West Hospital until the birth of my son. After a period of maternity leave, I took up my position here at the NSRI in March 2001. This position is funded by an NH&MRC Training Fellowship Grant.

Current research interest: Improving the evidence base for the practice of very early rehabilitation (AVERT)

Recent Publications:

2002 Bernhardt J, Matyas T, Bate P. Experience does not predict observation accuracy. Physiotherapy Theory & Practice (in press)
2001 Bernhardt J, Bate P, Matyas T. Training improves observation accuracy in novice clinicians. *Archives of Physical Medicine & Rehabilitation* 82; 1611-1618

2000 Wales L & Bernhardt J. A case for slow to recover rehabilitation services following severe acquired brain injury. *Australian Journal of Physiotherapy* 46; 143-146


1998 Bernhardt J, Hill K, Ellis P, Denisenko S. Serial changes in balance and mobility during rehabilitation following stroke. *Physiotherapy Research International* 3(2); 109-122

**NAME: LUCINDA BILNEY**

**Position:** Senior Public Health and Policy Officer

**Institution:** National Stroke Research Institute; National Stroke Foundation

**Contact Details:** C/- Boronia Building, Repatriation Campus; Austin and Repatriation Medical Centre; Banksia Street; West Heidelberg VIC 3081. Phone: 03 9496 2078; Mobile: 0402 261 210; E-mail: lucindabilney@telstra.com

**Qualifications:** Master – Business Administration; Bachelor – Applied Science – Orthoptics; Diploma of Applied Science – Orthoptics; Diploma of the Orthoptic Board of Australia

**Research Experience:** Project Manager – National Stroke Unit Program; Ophthalmology research including investigations into: Ocular Albinism; Congenital nystagmus mapping; Visual field evaluation in children following Vigabatrin; Ocular motor apraxia; and Strabismus surgery audit.

**Current Research Interest:** National Stroke Unit Program: This research project includes the development of a policy report identifying sustainable systems of care for managing stroke across regions or networks of health care providers, and the implementation of a feasibility study.

**NAME: DR AMY BRODTMANN**

**Position:** Research Fellow

**Institution:** National Stroke Research Institute, Austin & Repatriation; Medical Centre, Heidelberg, 3084

**Contact details:** Mobile 0417 569 803; email abrodtmann@hotmail.com

**Qualifications:** MB, BS, FRACP

**Research experience:** Completed six months of neurophysiology research examining recovery curves in patients with newly diagnosed idiopathic generalised epilepsy using transcranial magnetic stimulation (3) Enrolled in second year of PhD (see research interest below).

**Current research interest:** Functional magnetic resonance imaging of the human visual cortex in normal aging and following ischaemic infarction

**Relevant publications:**

2. Amy Brodtmann, Aina Puce, Ari Syngeniotis, David Darby, Geoffrey Donnan Hemodynamic response to faces remains stable until the ninth decade (Eighth International Meeting of the the Organisation for Human Brain Mapping, Sendai, Japan, June 2002)

**NAME: KEN BUTCHER**

**Position:** Stroke Research Fellow
Institution: Royal Melbourne Hospital

Contact details: kenneth.butcher@mh.org.au

Qualifications: B.Sc., M.D., PhD, FRCP(C)

Research experience: PhD, Neurophysiology (University of Western Ontario; 1990-95). Insular cortex of the rat: autonomic regulation by the insula, response to stimulation/stroke/lesions of the insula and neurochemistry of the sub-cortical nuclei mediating insular cortical responses; Post-doctoral Clinical Stroke Fellowship (Royal Melbourne Hospital; 2001-present). Diffusion/Perfusion weighted MRI in acute ischemic stroke and primary intracerebral hemorrhage.

Current research interests: Rational selection criteria for thrombolysis in acute ischemic stroke using MRI parameters; Characterization of ischemic pathophysiology and response to reperfusion using MRI in animal stroke models; Elucidation of mechanisms of secondary injury in primary intracerebral hemorrhage; Cardiac sequelae of acute ischemic stroke.

Relevant publications:

NAME: HEATHER CAMERON (FORMERLY H. M. O’MALLEY)

Position: Neurovascular Ultrasound Technologist

Institution: Dept of Neurology, ARMC

Contact details: ph: 03 9496 5216; 0407233893

Qualifications: RN; Accredited Medical Sonographer (Vascular)


Current Research Interest: Embolus Detection & Intracranial Large artery occlusive disease

Relevant Publications:

NAME: DR LEEANNE CAREY

Position: Senior Research Fellow

Institution: National Stroke Research Institute

Contact details: Level 1, Neurosciences Building, A&RMC; L.Carey@austin.unimelb.edu.au

Qualifications: BAppSc(OT), PhD

Research experience: Chief investigator on two NH&MRC grants, ARC small grant and other LaTrobe University and Austin Medical Research Foundation grants. Research active staff member and Senior Lecturer, LaTrobe University. Research Fellow/Senior Research Fellow, A&RMC and NSRI since 1995. Development of postgraduate distance education research subjects.


Relevant publications:


NAME: A/PROF BRIAN ROBERT CHAMBERS

Position: Associate Director and Head of Ultrasound Research
Institution: National Stroke Research Institute

Contact details: Austin & Repatriation Medical Centre, Heidelberg West, Victoria, Australia, 3081. E-mail: brc@bigpond.net.au

Qualifications: MBBS, MD, FRACP


Current research interest: 1996-Australian Urokinase Study (AUST) – Steering Committee; 1999-Dextran in Carotid Endarterectomy (DICE) – Steering Committee; 2000-2001Member PROGRESS Endpoint Committee; 2001-ARCH Steering Committee

Relevant publications:


NAME: DR HELEN MARGARET DEWEY

Position: Senior Research Fellow

Institution: NSRI

Contact details: Phone: 9496-2888, Fax: 9496-2650; Email: helend@austin.unimelb.edu.au

Qualifications: MB BS, PhD, FRACP, FAFRM (RACP)

Research experience: 1995-2000-Investigation of the epidemiological and health economic aspects of the major subtypes of stroke within a community based study (NEMESIS). This work lead to the award of a PhD from the University of Melbourne. 2000- Stroke epidemiology, outcomes, stroke rehabilitation and health economics research at the NSRI.

Current research interest: Stroke epidemiology, health economics and outcomes, stroke rehabilitation.
Relevant publications:


NAME: PROFESSOR STEPHEN DAVIS

Position: Professor of Neurology

Institution: University Melbourne/Director of Neurology, Royal Melbourne Hospital

Contact Details: Royal Melbourne Hospital, Email: stephen.davis@mh.org.au

Qualifications: MB BS 1972; MD 1985; FRACP 1980; FRCP (Edinburgh) 2002

Research Experience: Professor Davis has published over 150 papers, 20 book chapters, a text book on ‘Interventional Stroke Therapy’ (Blackwell Science 1998), and is co-author of a book in press on ‘Magnetic Resonance Imaging in Stroke’ (Cambridge University Press, 2002). He has chaired the Victorian Stroke Strategy (1997-2001) and served on numerous national and international committees. He has supervised 14 postgraduate students since 1991 and is the Head of Stroke Research and the Stroke MRI Laboratory at the Royal Melbourne Hospital. The MRI Stroke Research Laboratory involves a team of neurologists, neuroradiologists, physicists, a biostatistician and research fellows. He is a member of 4 editorial boards (Stroke; Cerebrovascular Disease; Journal of Neuroimaging and Journal of Clinical Neuroscience). He has given 30 invited overseas lectures and teaching courses in the past 5 years. He has served on numerous national and international steering committees for acute and secondary prevention stroke trials. He has had continuous NHMRC research support for the past 10 years and is currently a Principal Investigator on 3 NHMRC grants.

Current Research Interest: He has extensive experience in cerebrovascular research, with particular interests in acute interventional therapies, new magnetic resonance imaging techniques in brain ischemia, as well as secondary prevention and brain recovery.

Relevant Publications:


NAME: PROFESSOR GEOFFREY DONNAN

Position: Director

Institution: National Stroke Research Institute

Contact details: Level 1, Neurosciences Bldg, Repat; donnan@austin.unimelb.edu.au

Qualifications: MBBS, MD, FRACP

Research experience: Past Co-Chairman of the Australasian Stroke Trials Network. Author of over 200 publications in the field of stroke research and has edited/authored 3 books. Also involved in numerous national and international committees concerned with stroke. Main research interests are in clinical aspects of stroke.

Current research interest: Clinical aspects of stroke.

Relevant publications:


**NAME: DR AMANDA GILLIGAN**

**Position:** Research Fellow in Stroke Medicine

**Institution:** National Stroke Research Institute, A&RMC

**Contact details:** 03 94962856; gilligan@austin.unimelb.edu.au

**Qualifications:** MBBS (Hons) BSc FRACP

**Research experience:** ASK Trial clinical coordinator; Stroke Research fellow since 1998

**Current research interest:** Acute stroke therapies; Factors affecting hospital arrival following stroke

**Relevant publications:**


**Book chapters**


**NAME: PRAHLAD WEI SOON HO**

**Position:** Medical Student (AMS)

**Institution:** National Stroke Research Institute

**Contact details:** 9496-2527

**Current research interest:** Differentiation of Gray and White Matter in infarcts of neuroprotective trial patients.
NAME: DR DAVID HOWELLS

Position: NH&MRC Senior Research Fellow

Institution: Dept. Medicine, University of Melbourne. Associate Director, National Stroke Research Institute.

Contact details: Neuroregeneration Laboratory, Department of Medicine, University of Melbourne, Austin & Repatriation Medical Centre, Studley Road, Heidelberg 3084, Australia. Tel: +61 3 9496 3789, Fax: +61 3 9457 2654, email david.howells@unimelb.edu.au

Qualifications: B.Sc. (Hons), Ph.D.

Research experience: Diagnosis and therapeutic monitoring of variant forms of PKU characterised by severe neonatal catecholamine deficiency. The first mutation analysis allowing prenatal diagnosis in these diseases and the early treatment essential to prevent severe and irreparable brain damage. Demonstrated that CSF neopterins provide a useful clinical indicator of macrophage infiltration and activation in CNS disease. In extreme cases, macrophage activation can have profoundly damaging effects on serotonin metabolism. BDNF mRNA expression is reduced in the substantia nigra of patients with Parkinson’s disease suggesting a possible role in the genesis of Parkinson’s disease.

Discovered a new population of dopaminergic neurons which appear to proliferate in the striatum of patients with Parkinson’s disease. Demonstrated that dopaminergic sprouting occurs after physical injury to the striatum. Provided the first evidence for a physiological role for the potent dopaminergic neurotrophins BDNF and GDNF in adult animals - a role in spraying and regeneration. Discovered that activation of macrophages and microglia after injury to the striatum leads these cells to synthesis large amounts of GDNF and BDNF which regulate dopaminergic regeneration. Together with Peter Batchelor, proposed that failure of regenerating axons to grow across the lesion site occurs because of trophic arrest rather than just the presence of inhibitory factors or a glial limitans.

Current research interests: Axonal regeneration after CNS injury: Investigations into the role played by inflammatory responses and microglial and macrophage activation on control of axonal regrowth and collateral sprouting after CNS and spinal injury. Neuroprotection after spinal cord injury: Examining the neuroprotective effects of embryonic neural and notocord tissues from rat and quail after spinal injury in the rat. Dopaminergic plasticity in Parkinson’s disease: Determining the number, phenotype, function and origin of a new population of dopaminergic neurons discovered in Parkinson’s disease but not control striatum. The role of tPA in death of dopaminergic neurons: Using mice lacking expression of the tPA gene to examine the role of neural/microglial tPA production in the mechanism of dopaminergic cell death in the MPTP mouse model of Parkinson’s disease. The role of hypertension in induction of stroke: Determining whether hypertension or the small vessel disease it causes influences stroke size in rats and examining whether ACE inhibitors have their effects via reduction of hypertension or via direct effects on the CNS. Modelling the ischaemic penumbra after stroke: Using the hypoxic markers 3H- and 18F- FMISO to study role of the ischaemic penumbra in stroke evolution and to study the mechanisms of neuroprotection. Better animal models of stroke: Studying the effects of stroke in the brain of dwarf pigs which offer a large highly folded brain more similar to ours than the rats brain and studying the effects of hypertension and diabetes as co-morbidities after stroke in rats. Neuroprotection after stroke: Commercially funded research to investigate the neuroprotective properties of different drugs in our models of stroke.

Relevant publications:

9. Batchelor et al, Macrophages and microglia stimulate CNS peri-wound sprouting but prevent axonal growth across the lesion site. MCNE (In press, accepted 18/7/02).
NAME: INdra inDra

Position: Research Assistant/Computer Programmer

Institution: Neuroimaging Division, National Stroke Research Institute

Contact details: 94963114

Qualifications: Bach. Of Computer Science

Research experience: Currently doing honours research project

Current research interest: Currently doing honours research project

NAME: LOUISe JAMeS

Position: Stroke Nurse Consultant

Institution: Acute Stroke Care Unit-ARMC(Austin Campus)

Contact details: Email louise.james@armc.org.au, ARMC-Ward 7B ph.(03) 9496 5598 or pager 5598 via switch (03) 9496 5598, Fax: (03) 94963383

Qualifications: Registered Nurse Grade 3: Associate Nurse Unit Manager prior to Stroke Nurse Consultant Role.

Research experience: Involvement in Clinical Stroke Trials at a ward level.

Current research interest: Clinical Stroke Trials at a ward level.

NAME: BevyN Jarrott

Position: Professor and Head of Pharmacology

Institution: Monash University, Clayton Vic 3800

Contact details: Ph: 9905 5752; Fax: 9905 5851; E-mail: b.jarrott@med.monash.edu.au

Qualifications: Ph D (Cambridge 1969), BPharm (Qld 1965)

Research experience: 35 years experience in biochemical and neuro-pharmacology using animal models of disease such as hypertension and cerebral ischaemia

Current research interest: Development of novel neuroprotective drugs in animal models of neurological diseases; Helping to establish a research-based pharmaceutical industry in Australia

Relevant publications:


**NAME: MASATOSHI KOGA**

**Position:** Research Fellow  
**Institute:** Neuroimaging Unit, National Stroke Research Institute  
**Contact details:** mkoga@ff.iij4u.or.jp  
**Qualifications:** Medical Doctor  
**Research experience:** Ultrasound  
**Current research interest:** Ischemic penumbra  
**Relevant publications:**

**NAME: ERIN LALOR**

**Position:** Neurology Registrar  
**Institution:** ARMC  
**Contact Details:** Email: yongchem@yahoo.com; Mobile: 0411 531 609  
**Qualification:** MBBS, FRACP clinical/written examination  
**Relevant publications:**
Y. Lee, A. Schwarer, B. Day, Autologous peripheral stem cell transplantation as a treatment of severe peripheral neuropathy secondary to monogammopathy of unknown significance: A case study & literature review, Bone Marrow Transplantation, 2002; Vol 30 (1)

**NAME: YONG CHERN LEE**

**Position:** Neurology Registrar  
**Institution:** ARMC  
**Contact Details:** Email: yongchem@yahoo.com; Mobile: 0411 531 609  
**Qualification:** MBBS, FRACP clinical/written examination  
**Relevant publications:**
Y. Lee, A. Schwarer, B. Day, Autologous peripheral stem cell transplantation as a treatment of severe peripheral neuropathy secondary to monogammopathy of unknown significance: A case study & literature review, Bone Marrow Transplantation, 2002; Vol 30 (1)
NAME: CHRIS LEVI

Position: Staff Neurologist, Conjoint Senior Lecturer in Neurology, Director of Acute Stroke Services and Neurovascular Ultrasound

Institution: John Hunter Hospital, University of Newcastle

Contact details: Lookout Rd, New Lambton Heights, NSW, 2305. Ph 61 2 49213484 ; Fx 61 2 49213488

Research experience: 12 months tenure as clinical co-ordinator of the Australian Streptokinase Trial. Chief investigator involved in the design, conduct and successful completion of the Dextran in Carotid Endarterectomy (DICE) trial. Member of three on-going large multicenter investigator–driven clinical trials, DICE, ARCH and Stroke Thrombolysis-MRI. Local investigator in international multicenter secondary stroke prevention trials, CAPRIE, BRAVO, MATCH and VITATOPS. Local investigator in the international multicenter acute stroke trials ECASSII and ASTIN.

Current research interest: Working in the field of cerebrovascular disease research over the past 9 years with major interests being in clinical applications of neurovascular ultrasound, acute stroke therapies, antithrombotic therapies, and stroke prevention.

Relevant publications:


NAME: GABRIEL LIBERATORE

Position: Research Fellow (NH&MRC)

Institution: University of Melbourne

Contact details: 9496-3257 (work) 0414 463956 (mobile)

Research experience: Upon completion of my Bachelor of Science (Biochemistry) degree with honours year at the University of Melbourne, I undertook a Ph.D. research program studying mechanisms of neuroregeneration in Parkinson's disease within the Department of Medicine/Neurology at the University of Melbourne (A&RMC). After completing my Ph.D. in early 1998, I was employed as a Post-Doctoral Research Fellow in the Department of Neurology, Columbia University, New York focusing the mechanisms that underlie neurodegeneration in Parkinson’s disease. Upon my return to Australian I was appointed as a Research Fellow in the Department of Medicine/Neurosciences, Box Hill Hospital, Monash University to head up the Basic Science Unit within the Department of Neurosciences studying the neurotoxic mechanisms of tissue plasminogen activator (tPA) and Ischaemic stroke. Upon joining the Dept of Medicine/Neurology (A&RMC) in September 2001 I have continued to work on neuroregeneration/neuroprotection aspects of ischaemic stroke in animal models.

Current research interest: My current research interests lie in understanding the mechanisms that lead to tPA neurotoxicity in addition to the evaluation of novel neuroprotectants in animal models of ischaemic stroke.

Relevant publications:


NAME: HENRY MA

Position: Neurology Registrar

Institution: Austin & Repatriation Medical Centre

Contact: 26 Barton street, Doncaster East, Melbourne, Victoria 3109. Tel (03) 98421924;

Qualification: MBBS (Melb), Part 1 FRACP


NAME: DR ROMESH MARKUS

Position: Neurologist & Research Fellow
Institution: National Stroke Research Institute

Contact details: 03 9496 2627 (Tel); 03 9496 2650 (Fax); markus@austin.unimelb.edu.au

Qualifications: MBChB FRACP

Research experience: Undertaking PhD at the University of Melbourne

Current research interest: Imaging the ischaemic penumbra in acute stroke

Relevant publications:


NAME: MARJORY MOODIE

Position: Research Fellow

Institution: National Stroke Research Institute

Contact Details: Centre for Health Program Evaluation, Level 3, Boronia Building, Repatriation Campus, Austin and Repatriation Medical Centre. Phone: 03 9496 4425; E-mail: marjory@pgrad.unimelb.edu.au

Qualifications: Bachelor of Arts (Hons); Diploma of Education; Diploma of Town and Regional Planning; Doctorate of Public Health (in progress)

Research Experience: Planning for and evaluation of health service programs and delivery models

Current Research Interest: Application of MORUCOS model for priority setting in stroke – ascertaining the incremental cost-effectiveness of interventions across the stroke pathway compared to current practice. Economic evaluation of stroke care delivery models for SCOPES study and the National Stroke Unit Program.

NAME: THANH PHAN

Position: Stroke Fellow

Institution: NSRI

Contact details: phantg@austin.unimleb.edu.au

Qualifications: FRACP

Research experience: Stroke

Current research interest: Stroke
Relevant publications:

1-Friend KL, Crimmins D, Phan TG, Sue CS, Colley A, Fung VSC, Morris JGL, Sutherland GR, Richards RI. Detection of a novel missense mutation and second recurrent mutation in the CACNA1A gene in individuals with EA-2 and FHM. Human Genetics 1999; 105: 261-265


3- Koh M, Phan TG, Atkinson JLD, Wijdicks EFM. The role of neuroimaging in the management of cerebellar infarct with mass effect. Stroke 2000: 31; 2062-2067


9-Koh M, Phan TG, Wijdicks EFM. The surgical management of cerebellar infarct with mass effect. The Neurologist May 2000

10-Phan TG, Wright PM, Markus R, Howells DW, Davis SM, Donnan GA. Salvaging the ischaemic penumbra: more than just reperfusion? Clin Exp Physiol Pharm 2002; 29: 1-10

NAME: BRUNO PEDREIRA

Position: Stroke Registrar

Institution: Austin & Repatriation Medical Centre

Contact details: 03-9496-5000 (page)

Qualifications: MD

Relevant publications:

Pedreira B, Azevedo A. Action, mechanisms and effects of cocain at the Central Nervous System. Escola de Medicina e Saúde Pública. 1995

Bacellar A, Muniz AL, Jesus PA, Pedreira B, Costa G, Azoubel AC, Vidal da Cunha L. Cerebrovascular Diseases Subtypes in patients at São Rafael Hospital. IV Update and Research Seminar – Hospital São Rafael, Salvador, BA. 1996

Lessa I, Pedreira B. Reality of attention to diabetic patients at emergency department with acute Cerebrovascular disease. 22º Brazilian Congress of Endocrinology & Metabolology, Salvador, BA. 1996

Lessa I, Pedreira B. Validation of DM as referred morbidity in acute Cerebrovascular disease urgencies. 22º Brazilian Congress of Endocrinology & Metabolology, Salvador, BA. 1996

Lessa I, Pedreira B. Estimative of frequency of DM in patients with acute Cerebrovascular disease by capture-recapture method. 22º Brazilian Congress of Endocrinology & Metabolology, Salvador, BA. 1996
NAME:  TANYA REDMAN

Position:  Clinical Trials Coordinator

Institution:  National Stroke Research Institute

Contact details:  Level 1, Neurosciences Building, Repatriation Campus; Austin & Repatriation Medical Centre; 300 Waterdale Road; Heidelberg Heights, Victoria 3081. Phone: +613 9496 5303; Fax: +613 9496 2650; Email: tanya.redman@armc.org.au

Qualifications:  Graduate Certificate of Nursing (Critical Care) 1999; Bachelor of Nursing 1994

Research experience:  Clinical Trials Coordinator, NSRI 2001 - present

Current research interest:  Acute stroke trials

NAME:  SASITORN SIRITHO

Position:  Stroke Research Fellow

Institution:  National Stroke Research Institute

Contact details:  Level 1, Neurosciences Building, Repatriation Campus; Austin & Repatriation Medical Centre; 300 Waterdale Road; Heidelberg Heights, Victoria 3081. Phone: +613 9496 2527; Fax: +613 9496 2650; Email: siritho@yahoo.com

Qualifications:  MD


NAME:  KARIN SITTE

Position:  Manager, Austin Node

Institution:  Neurosciences Victoria

Contact details:  NSRI, Neurosciences Building, ARMC, Banksia St, West Heidelberg, Vic 3081. Ph: (03) 94962948, email: Karin.sitte@neurosciencesvic.com.au

Qualifications:  BSc (hons), PhD

Research experience:  Immunogenetics, vaccine technology, molecular biology, gene therapy for neurological diseases and cell biology

Current research interest:  Although my background is in medical research I am interested in management of research and innovation. Interests are in fostering collaborative research in neuroscience to maximise commercial outcomes and thus help fund future research.
Relevant Publications:


NAME: RACHEL THORPE

Position: Project Officer

Institution: Public Health Division, National Stroke Research Institute

Contact details: Level 1, Neurosciences Building; Austin and Repatriation Medical Centre; Banksia Street; Heidelberg West, VIC 3081. E-mail: rachel@strokefoundation.com.au; Phone: 9496 2081; Mobile: 0403 253 907

Qualifications: B.Sc (Hons); B.HealthSc (Naturopathy)

Research experience: Project Coordinator SCOPES II (Stroke Care Outcomes Providing Effective Services II).

Pharmacological research into:
• Interactions between omega-3 fatty acids and antiarrhythmic drugs
• Effects of omega-3 fatty acids on cytokine production by monocytes

Clinical Research:
• Coordinating Phase 1 Bioequivalence/Bioavailability Clinical Trials
• Coordinating Phase 3 and 4 Clinical Trials of Blood Products

Current research interest: SCOPES II project: This project is investigating the long term outcomes of stroke in an existing cohort of stroke survivors and carers. The major research focus is prevalence of Sleep Disordered Breathing and associated risk factor variables 3 years post stroke.

NAME: MANDY THRIFT

Position: Head of Epidemiology Division

Institution: National Stroke Research Institute

Contact details: Email thrift@austin.unimelb.edu.au Phone 9496-2862, Fax: 9496-2650

Qualifications: BSc(Hons), PhD


Current research interest: Is to improve knowledge about long-term outcome after stroke, and to determine the accuracy of death certificate information for stroke.

Relevant publications:

1. Thrift AG, McNeil JJ, Forbes A, Donnan GA. Three important subgroups of hypertensive persons at greater


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**NAME: JOHN WILLIAMS**

**Position:** MR Physiologist

**Institution:** The Howard Florey Institute of Experimental Physiology and Medicine

**Contact details:** Phone: +61-3-8344-7087; Fax: +61-3-9348-1707; Email: j.williams@hfi.unimelb.edu.au

**Qualifications:** BSc, PhD

**Research experience:** Planning and manufacture of Surface coils (single- and double tuned) for *in vivo* (brain, skeletal muscle, heart, liver) and *in vitro* (isolated hearts) applications in rats; Coordination of ethics applications and physiological protocol development for all experiments active at The Howard Florey Imaging facility; 10 years experience running Varian NMR spectrometers (both spectroscopy and imaging); four years spent administering console use, set-up, upgrades, troubleshooting, and repairs; 4 years experience with Bruker systems (Biospec 47/30 DBX, AMX300 &400); = 13 years experience preparing and running *in vivo* NMR experiments with physiological monitoring; Member of the Society for Cerebral Blood Flow and Metabolism; Member of the International Society for Magnetic Resonance in Medicine.

**Current research interests:** Diffusion-weighted and Tensor imaging, functional imaging of homeostatic functions, Neuroprotection in MCAO stroke.

**Relevant publications:**


NAME: DENNIS YOUNG

Position: Clinical Trials Coordinator

Institution: National Stroke Research Institute

Contact details: Level 1, Neurosciences Building, Repatriation Campus; Austin & Repatriation Medical Centre; 300 Waterdale Road; Heidelberg Heights, Victoria 3081. Phone: +613 9496 2648; Fax: +613 9496 2650; Email: dyoung@austin.unimelb.edu.au

Qualifications: Graduate Certificate of Nursing (Critical Care) 1996; Certificate of Nursing 1985; Associate Diploma of Welfare studies 1979; Diploma of Arts 1976

Research experience: Research Nurse, Nemesis 1997 – 2000; Clinical Trials Coordinator, NSRI 2000 - present

Current research interest: National Coordinator for: Dextran in Carotid Endarterectomy (DICE) Study; Aortic arch Reduced Cerebral Hazard (ARCH) Study
Awards Presented at the Retreat

The Spouse Award was presented to Roger Evans for not only being the only spouse to attend the scientific sessions but actually asking a question.

The Most Thoughtful Spouse Award was presented to Roger Evans for having a spa to avoid listening to Mandy moaning whilst she was having a massage.

The Marathon Man Award was presented to Chris Levi and Stephen Davis for actually going for a run (not just talking about it).

The Sports Award was presented to Amanda Gilligan for pulling her monkey muscle within 5 minutes of play on the tennis court.

The Medical Journal of Australia Award was presented to Leeanne Carey for most appropriate use of a medical journal: providing traction for bogged vehicle.

The Orienteering Award was presented to Romesh Markus and Brian Chambers for turning a 5km walk into a 10km cross-country survival trek.

The Optus Award was presented to Bevyn Jarrott for answering “Yes” to a searching question during discussion.

The Pyrenees Sobriety Award was presented to Anne Abbott for passing breathalyser test en route.

The Most Frequent Attendance Award was presented to Henry Ma for commuting between Warrenmang and Melbourne for job interviews.

The Get Smart Award was presented to Fred Mendelsohn for best use of spy gadgetry (ie miniature camera) in a social setting.

The Best Utilisation of Warrenmang Facilities Award was presented to Mandy Thrift for use of facilities including spa, massage, tennis, wine tasting, and bush walking.

Congratulations to all the winners!