Basic Science

Clinical Interface

Second Annual

Stroke Research Retreat

10th to 12th October 2003

Maryland Country House, Marysville

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

2003

‘Basic Science Clinical Interface’

Facilitator
Professor Edward Byrne
Professor Edward Byrne

Position and Institution: Executive Dean of Medicine, Faculty of Medicine, Nursing & Health Sciences, Monash University

Qualifications: MBBS (First Class Hons), BMedSci, Diploma of Medical Science, MD, DSc, FRCP, FRACP

Research Experience: Over 20 years of research leadership in neuromuscular diseases, with major breakthroughs in the understanding of human mitochondrial cytopathies and contributions to the field of muscular dystrophy. Some 200 research papers and 20 doctoral students supervised. Current research interests: mitochondrial cytopathies, muscular dystrophies, motor neurone disease.

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Acknowledgements

Sponsors of the National Stroke Research Institute
Second Annual Stroke Research Retreat

Aventis Pharmaceuticals Pty Ltd (Roy Gustini & Gilbert Nichele)

Boehringer Ingelheim Pty Ltd (Henrietta Pitsilis)

CSL (Dr Russell Basser & Marcus Kalousek)

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Servier Laboratories Pty Ltd (Michael Bendle)
FOREWORD

Following the success of our initial retreat it was only natural that we would want to continue the tradition. This year’s venue at Marysville is again ideal in that we are able to get away from the everyday distractions of work and focus on what we have achieved over the preceding 12 months and plan our future directions. Indeed, the most important benefit of our retreat program is the generation of new ideas and development of new collaborations. As before, we have been benefited by the attendance of collaborators from almost every state in Australia as well as New Zealand. Also, we are fortunate to have on our NSRI staff many people from different parts of the world who bring their own experiences to the table which is of benefit to us all. We continue the “vertically integrated” approach to our research from the basic sciences through to public health. The retreat certainly helps us with the integrative process so that each division and collaborating groups is aware of the activities of others.

We are very fortunate in having the expertise of an outstanding facilitator for this years retreat. Professor Edward Byrne, Neurology, Neuroscientist and administrator has been a major contributor to the neurosciences in this country. Having now moved from his position as Director of the Centre for Neuroscience at Melbourne University to that of Dean of Medicine at Monash University, he is particularly well qualified to facilitate events such as this. We appreciate his involvement enormously.

Our sponsors form an integral part of the retreat and it is nice to see so many representatives here again. The ongoing relationship between academia and the commercial world is an important one for the betterment of science generally.

We thank you for your involvement in what is an important part of the NSRI activities.

GEOFFREY A. DONNAN
### Participants

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POST-RETREAT REPORT FROM FACILITATOR PROFESSOR EDWARD BYRNE

This two day workshop brought together a series of outstanding investigators covering all key aspects of stroke research. The strengths of this program, arguably the single strongest disease orientated neuroscience program in Australasia, rests on a number of strong foundations which were apparent to me as a facilitator.

Firstly, the fact that there is genuine interaction between basic scientists and clinicians with a sharing of ideas and an understanding of the questions and dilemmas that face either group by the other. This bodes well for the future in the development of increasingly powerful translational research at the basic science clinical interface.

Secondly, in both basic and clinical research, but especially the latter, the Stroke Group has been successful in nurturing a number of outstanding senior investigators who interact well, and together are able to bring a major intellectual force to bear on important problems.

Thirdly, the group is well aware of research progress internationally and focuses its resources and attention on areas where it has a high international competitiveness and is very likely to be able to make a difference. The focus is therefore international rather than national, with a significant chance that advances will be made that alter practise in stroke medicine worldwide.

Finally, the quality of the leadership brought to the activity by Professor Geoffrey Donnan and his Royal Melbourne Hospital colleague, Professor Stephen Davis is manifest, and following their example, there is a high and an appropriate degree of mutual respect among the key stroke investigators, that is they genuinely like and respect each other, that also bodes well for a long and successful stroke program in Australasia.

I greatly enjoyed facilitating the meeting and wish the stroke community stellar success in the years ahead.
POST-RETREAT REPORT FROM DIRECTOR PROFESSOR G.A. DONNAN

The retreat for this year was, again, a most rewarding experience from both the academic and social point of view. All research is facilitated greatly by personal contact and from this may come great ideas. The structure of the program certainly allowed this to occur. With only 4 to 6 minutes for presentation in a 20 minute timeslot, the majority of time was spent in discussion which is the main object of the exercise. Retreats need to be like this, and quite unlike any of the numerous formal meetings which many of us attend.

Professor Ed Byrne was an outstanding facilitator. His urbane wit and breadth of knowledge across a broad area of the neurosciences allowed everyone to become involved. I am sure these skills will be equally useful in his new role as Dean of Medicine at Monash University. On your behalf I thank Ed Byrne for making the Retreat such a success.

Also deserving thanks is Brian Chambers who, together with Anita Thompson and Karin Sitte were the real drivers behind the organisation of this retreat. The conduct of the whole event was in no small part due to their efforts.

Much was discussed, and even more ideas were generated. Success indeed!

GEOFFREY A. DONNAN
The Second Annual Stroke Retreat was testimony to the broad range of collaborations and research interest of NSRI. Representatives of collaborating centres from Royal Melbourne Hospital and the Howard Florey Institute (Vic); Gosford Hospital, St Vincent's Hospital and John Hunter Hospital (NSW); Menzies Research Institute (TAS), Waikato Health (NZ) and Royal Brisbane Hospital (QLD) attended to share their latest research results with colleagues at NSRI.

This year proceedings were facilitated by Professor Ed Byrne who highlighted the expected outcomes of this retreat as building team morale, gaining a competitive edge for the Institute and its collaborators, and foster innovative ideas from interaction between different disciplines.

The format for the retreat was modified from the previous year by limiting presentations to 4 slides in order to maximise discussion time. In addition participants from different disciplines were encouraged to ask questions to foster lateral thinking and greater cross-discipline involvement. The purpose of this report is to capture these discussions.

Epidemiology and Public Health

Mandy Thrift started with a presentation on NEMESIS outcomes and future directions, particularly NEMESIS 2. The main discussions of this topic centred around 4 main issues:

1. Quality of regional centres to provide stroke services and how the development of services will impact on the study. The outcomes of the study may change as services are improved.

2. Genetic issues: No genetic data was collected for NEMESIS 1, however in studies in Iceland this type of data was collected and it lead to the discovery of a gene associated with stroke. A TPA polymorphism has also been reported in a study from Adelaide. A suggestion was made to include DNA data in NEMESIS 2, this would require setting up a DNA bank and ethical issues need to be explored and resolved.

3. How stroke mortality risk factors will be looked at in NEMESIS 2. This could be achieved on a geographical basis, which would need to be set up prospectively. This issue will be difficult to address because mortality is falling but there is not sufficient longitudinal data and results have been conflicting. Some of these questions may be answered through the International Stroke Incidence Study Data Pooling Project where data from different geographical locations will be pooled to increase the power of the analysis

Helen Dewey discussed the development and application of a ‘Model of Resource Utilisation, Costs and Outcomes for Stroke’ (MORUCOS). This model incorporated data collected through NEMESIS. This model is particularly useful for the economic comparison of different treatments and therefore assists in the allocation of resources across stroke pathways. For example, in a study comparing thrombolysis and aspirin as treatments, thrombolysis was shown to be more economical. This seems counterintuitive but as the model shows, thrombolysis is very effective and patients can go home after therapy therefore the cost of caring for patients long-term is reduced considerably.
Potentially this model could be marketed to the Pharmaceutical industry as it allows more flexibility than the traditionally used models. There is a need to work very closely with the pharmaceutical industry to ensure a good understanding of the assumptions used in this model.

Jonathan Sturm presented his plans to conduct an observational study on mood impairment after stroke with the ultimate aim to identify predictors of these conditions. Several issues to take into consideration in this study were identified:

1. The question in this study is quantitative rather than qualitative. It is well known that post-stroke depression affects outcome, therefore it is important to establish if intervention can improve the outcome.

2. Confounding factors such as frontal lobe impairment need to be taken into account. It is essential to establish if the mood impairment is the result of having a stroke or actual impairment due to injury.

3. The neurochemistry of antidepressants might be worth looking at as they may have neuroprotective effects depending on which cells are affected by the stroke.

4. The effects of changes in social support and resource utilization need to be taken into account.

The topic of dementia and links with vascular disease was discussed by Velandai Srikanth. Stroke is an endpoint of vascular disease but cognitive impairment is not necessarily the result of stroke. This is a critical topic as the population is aging. There is a need to understand the natural history of how stroke can lead to cognitive decline, hence cohort studies are required. Intervention studies to date have resulted in conflicting results. There are questions on how best to address this topic. One option would be to do a large study looking at many outcomes and then teasing cognitive impairment out. This approach may be too complex and requires a prospective group of patients to be followed over a long period of time. An alternative is to use specific groups of patients, for example patients that develop a progressive dementia type illness. Unfortunately these patients are not very common. Another approach would be to use the Tasmanian cohort which includes 4000 patients of which over 60% are in the correct age group. This group is also the only one in the world to include pedometer measures. The only problem with this cohort is that there may not be sufficient statistical power. There are possibilities for collaborations to validate key tests specific to dementia and also to perhaps include MRI data.

Christopher Levi and Dominique Cadilhac completed the session by discussing Stroke Units roll-out and evaluation. The government is not convinced that stroke units are effective, therefore information on access and outcomes is required to mount a convincing argument. The Government takes information from other countries on board but they still want local evidence. Even with good local evidence, agendas change, buck-passing and funding cuts occur. A groundswell from clinicians and public usually ensures a response.

Currently outcome monitoring pre and post implementation is being carried out by NSRI. Discharge summaries are being used for tracking of stroke complications. One option that has been tried for implementation is to use the hospital accreditation services, this may need further investigation. Implementation in more remote areas is restricted by geography and
telemedicine has proved to be of limited use. Roll-out of units is best achieved progressively from cities to regional centres.

**Basic Science**

David Howells provided an introduction to this session on some of the difficulties in translating animal research to clinical research.

Translational research is very important for clinical researchers. Clinical trials use global test statistics which may not be feasible in animal studies. Usually animal studies use small numbers. The statistical power can be increased by conducting several tests. The result is that usually only gross effects can be observed as opposed to human trials. Another problem is the difficulty in measuring cognitive effects and some progress is being made to develop these for the dwarf pig model. Training is another effect that is seen in animal studies. In human studies a long period of time elapses between tests and this “training” effect is not seen.

This introduction was followed by two presentations on specific treatment strategies and their mechanisms of action. Gabriel Liberatore discussed the advantages and disadvantages of tissue type plasminogen activator (tPA) and its mode of action in different animal models. Cytotoxic effects were observed with tPA in specific mouse models, this may have implications for human therapy. The cause of this cytotoxic effect is not understood. Theoretically the neuroprotective cascade is similar in rats and humans, and the experiments were carried out with human tPA. Further experiments are required to determine if this effect translates to humans and other animal models such as sheep and dwarf pigs.

Bevyn Jarrott followed last year’s theme of looking for potential neuroprotectants among naturally occurring substances that are known to be safe. One such substance is caffeinol, a combination of caffeine and ethanol (2 espressos and a double scotch!). This presentation resulted in a humorous discussion. The problem with this approach is that it is unlikely to get support from pharmaceutical companies because these substances cannot be patented. A trial using caffeinol is already underway in Texas and preliminary work on the pharmacokinetics is also being done. This makes it more difficult for our groups to jump on the bandwagon.

Another alternative is vitamin K and Activated Protein C, both endogenous substances that appear to have neuroprotective action in rodent models. One advantage of using vitamin K is that it can be used without the need for toxicology data.

Neil Spratt presented further data on the use of $^{18}$F-MISO as a marker for the penumbra. The fundamental question is whether F-MISO does indeed bind to tissue that destined to infarction without intervention. Intervention in this case is reperfusion after infarction. Perfusion index is measured using a laser Doppler, although spontaneous reperfusion can occur. It was suggested that double label autoradiography could be done in addition to laser Doppler monitoring, however it is not clear at this stage if this approach is feasible. It was also suggested that DWI imaging could be included in this project (as used in humans). Access to the MRI could be limiting factor and is perhaps better done as a separate follow on experiment. Characterisation of the cells in the penumbra would also be useful as it may
shed some light on what cell populations are most affected. The level of metabolic activity of different cell types may affect their vulnerability.

The final presentation in this session was given by Tori O’Collins on an example of translational research. Neuroprotective drugs will be identified in the literature and tested in various combinations on animal models to then develop clinical protocols for use early after ischemic or haemorrhagic stroke. An ambitious project, as it focuses on multimodal therapy as opposed to single drugs. This is a strategy that has worked well with AIDS and cancer. There is a lot of work involved in using drugs in combination as a good understanding of toxicology is required before human trials can commence. On one hand this approach is also attractive to pharmaceutical companies as it may result in powerful drugs, on the other hand, there are problems associated with patenting once drugs are used in combination. This is an area where natural compounds such as suggested by Bevyn Jarrott may have an advantage. There are also some regulatory hurdles to overcome. It may be difficult to justify the use of experimental therapies in combination with others when they have not been effective on their own.

Imaging

Peter Wright introduced this topic by discussing the gold standard for imaging of the penumbra. A penumbra marker needs to be able to identify salvageable tissue and show a clinical correlation with the natural history of stroke and intervention. MRI is reasonably validated for clinical and imaging outcomes but it has been difficult to obtain quantitative values and thresholds at certain time points. To date $^{15}$O-PET is still considered to be the gold standard and the best validated technique. F-MISO is the second best validated technique. MR and BOLD could be good techniques in the future as they correlate well with $^{15}$O-PET. One problem is that there are different definitions and ways to look at the penumbra and a gold standard may not be appropriate. There is still a lot of work to be done on quantitation and ultimately clinical validation.

Romesh Markus presented the use of 18F-MISO penumbragram’s as a method to study the changes in spatial distribution of the penumbra with time from ischemic stroke onset. This method can be applied to determine differences in penumbral characteristics between white matter and grey matter and also to determine metabolic characteristics of abnormal regions identified by MRI techniques. The discussion following the presentation focused on alternative methods to image the penumbra: Astrocyte markers (not suitable as whole hemisphere can get activated), microglial markers (specific to injured tissue), apoptotic markers (only become visible at the end of the cascade when tissue is near death), MR studies (need homogenous cohorts resulting in small sample size). The advantage of the penumbragram approach is that heterogenous patients can be used for the study, increasing the sample size. Another possible approach would be to calculate a ratio of infarcted tissue (using appropriate markers) and penumbral tissue (using penumbral marker). High field MRS where methyl groups become visible may be useful in visualising a perfusion deficit appearing/disappearing and could be used as an apoptotic marker. It is still not clear whether penumbral tissue is apoptotic or necrotic. Animal models seem to favour apoptosis as a mechanism of action.
Ken Butcher addressed the question of blood flow changes in haemorrhagic stroke using imaging techniques. In intracerebral haemorrhage, imaging reveals that oedema occurs fairly early on and hypoperfusion resolves spontaneously. ADC maps show increased movement of water which is not consistent with ischemia and is most likely plasma derived oedema. This study highlights the need for a better understanding of the mechanisms underlying oedema in order to perform relevant interventional studies to lower blood pressure. The best surrogate outcome measure for clinical studies seems to be volume. DWI and PET measures are useful in experimental studies but for clinical studies a very fast measure is required. SPECT was attempted but it was difficult to recruit sufficient patients.

Queensland collaborator Michael Walsh highlighted some of the imaging techniques being used in his laboratory to gain a better understanding of the penumbra, these include high density EEG together with MRI, sodium imaging and Phosphorous MRS. Sodium imaging and phosphorous imaging can be used to compare extracellular and intracellular concentrations. MRS can be used to look at lactate and ATP almost like a tissue clock depicting the severity of oxygen deprivation over time. The core of a DWI lesion is undergoing oxidative metabolism where ATP is low and lactate is high. Towards the edge of the penumbra ATP supplies increase and lactate decreases. It appears that under normal conditions neurons that are further from capillaries and also microglia can use lactate anaerobically. The effect of lactate in chronic stroke is not fully understood, however it is possible that penumbral cells that survive beyond 24 hours can use glycolysis to prevent apoptosis. Lactate is generally low in neural tissue because of the lack of glycogen but one possible source is from microglia.

Rachel Mulligan presented preliminary data on the development of new PET radioligands to image apoptotic tissue in stroke.

Clinical Trials

Geoff Donnan discussed the future of clinical trials of neuroprotectants and expanded on the theme of Time Window in Neuroprotection (TWIN) presented earlier by Tori O’Collins. The aim of this study is to combine several neuroprotective therapies and provide them early after stroke possibly even by paramedics. The discussions following the presentation explored combining neuroprotective therapies with other treatments such as inducing hypothermia. The consensus was to keep the study simple by using treatments that are easily administered such as caffeinol, nicotinamide and minocycline. Lessons learned from AIDS and cancer therapy support this approach, where mixing of several different drugs have led to complications and adverse events.

Malcolm Macleod continued with the theme of multiple therapies and presented a tool to select drugs to enter the TWIN study. Malcolm performed a stratified meta analysis to compare different drug studies using animal models. Traditionally animal models have been used for proof of concept studies followed by pathophysiology studies in humans before returning to animals to test efficacy. This process is very time consuming and even using cellular models before animal models has not always resulted in drugs that work in humans. A better approach might be to do the pathophysiology and efficacy studies in animals before
entering human trials. This raises the question of demonstrating a process before arriving at a drug target. The flip side of this argument is that there are many drugs on the market where the mechanisms of action are unknown.

Progress on the first randomised controlled early rehabilitation trial was presented by Julie Bernhardt. Questions were asked about the experiences in Trondheim (Norway) with regards to stroke unit care versus general hospital ward care. There are significant differences between the models used in Trondheim and our stroke units; Julie is currently in the process of dissecting out what the differences are. It was suggested that patients for this trial should be randomised by week rather than by patient to ensure patients are blinded as to which group they are assigned to.

Louise Allport described results of a study to determine if the insular cortex (IC) is involved with hyperglycaemia in stroke. Hyperglycaemia was correlated with IC injury with no differences seen in glycemic state and time of stroke between diabetic and non-diabetic cases. Also, the correlation between volume and blood glucose disappears when the insular cortex is involved. It is not clear from this study if it is a correlation rather than causality. It may be possible that the IC is more susceptible to higher glucose levels. Animal studies do indicate that injury to the IC results in an increased stress response (neuroendocrine dysregulation). This study raises the possibility of considering the administration of insulin early in stroke.

Finally, Stephen Davis reported on progress with the EPITHET trial, an investigator driven trial to determine if perfusion-diffusion MRI can be used to identify responders to rt-PA beyond 3 hours. The ensuing discussion was centred around MR based surrogate outcomes and how looking at infarct growth as a surrogate marker could make neuroprotection studies simpler and more amenable to large numbers of patients.

The humorous side of proceedings – memorable quotes

“Anyone disobeying the 4 slide rule will be sent home along with anyone wearing a tie” – Geoff Donnan

“…you can say silly things that you would not say at an international conference which of course won’t be held against you except by Geoff who does your annual performance review” – Ed Byrne

“The one thing about stroke units is that they are a winner!” – Chris Levi.

“In basic science we don’t talk about qualitative research rather semi quantitative research” – Ed Byrne

“Anybody tried a diuretic on neuroprotection? “Alcohol, caffeine and cold would certainly have an effect on me” – David Howells (in relation to caffeinol study)

“Apoptotic cells are like sheep on a ship on the way to the Middle East being herded to a cliff” – Malcolm Macleod.
# NSRI RETREAT PROGRAM - 2003

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<td>Welcome drinks 6.30 for 7.00pm</td>
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<td>BREAKFAST to 8:00am</td>
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<td>8:20am</td>
<td>G. Donnan -</td>
<td>Welcome and overview.</td>
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<tr>
<td>8:50am</td>
<td>A. Thrift -</td>
<td>Nemesis: Where to Now?</td>
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<td>9:10am</td>
<td>J. Sturm -</td>
<td>Health Economics: From Models to Policy.</td>
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<td>9:30am</td>
<td>V. Srikanth -</td>
<td>Stroke Outcomes: Do Sub-types Matter?</td>
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<td>9:50am</td>
<td>C. Levi -</td>
<td>Post Stroke Dementia: Does it Exist?</td>
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<td>10:10am</td>
<td>D. Cadilhac-</td>
<td>Rolling Out Stroke Units.</td>
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<td>How do we evaluate Stroke Units?</td>
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<td><strong>Sunday 12th</strong></td>
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<td>BREAKFAST to 8:30am</td>
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<td>9:00am</td>
<td>P. Wright -</td>
<td>Which Outcomes in Animal Models in Stroke?</td>
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<td>9:20am</td>
<td>R. Markus -</td>
<td>Penumbra in ischaemic and haemorrhagic stroke.</td>
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<td>9:40am</td>
<td>K. Butcher -</td>
<td>Perfusion thresholds and the effects of thrombolysis.</td>
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<td>10:00am</td>
<td>M. Walsh -</td>
<td>MRI: Beyond diffusion and perfusion.</td>
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<td>10:20am</td>
<td>R. Mulligan -</td>
<td>New PET ligands in stroke.</td>
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<td><strong>Main Topic</strong></td>
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<td>11:10am</td>
<td>G. Donnan -</td>
<td>Where to now with clinical trials? (TWIN etc.)</td>
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<td>11:30am</td>
<td>M. MacLeod -</td>
<td>Rodents are little people.</td>
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<td>11:50am</td>
<td>J. Bernhardt -</td>
<td>All about AVERT.</td>
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<td>12:10pm</td>
<td>L. Allport -</td>
<td>Hyperglycemia and stroke: new insights.</td>
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<td>12:30pm</td>
<td>S. Davis -</td>
<td>EPITHE.</td>
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<td>12:50pm</td>
<td>Closing -</td>
<td>Stephen Davis &amp; Brian Chambers</td>
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<td>LUNCH &amp; DEPARTURE 2.30pm</td>
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**Background:** Although stroke is a major cause of mortality and disability, little is known about the long-term outcome of stroke patients in Australia. There has also been very limited information about the financial costs of stroke. To address these issues we have been following up 1,687 stroke patients (1,843 events: 1,336 first-ever strokes, and 507 recurrent strokes) from the North East Melbourne Stroke Incidence Study (NEMESIS) to 5 years.

**Progress to Date:** This is an epidemiological study in which the 'ideal' criteria for stroke incidence studies have been utilised. Incidence of stroke and its subtypes has been assessed. Assessment of long term outcome (recurrent stroke, quality of life, dependency, and survival), costs of stroke, and adequacy of management of risk factors is continuing. Five year interviews will be completed in May 2004.

**Future Directions:**
- **10-year follow-up of NEMESIS.** We have applied for funding to continue following patients up to 10 years (survival, stroke recurrence, disability, handicap, quality of life, costs).

- **International Stroke Incidence Study Data Pooling Project.** This is an initiative from the Oxford Vascular Group. The data from eight studies (Italy, Scotland, England, and Australia) will be pooled to enable us to investigate incidence (by region), survival, stroke recurrence, risk factors, and outcome (disability, handicap, etc.). We are interested in investigating short and long term outcome of intracerebral haemorrhage, incidence of subtypes (ICH, SAH, and CI) between different ethnic groups, 28 day and long-term outcome (e.g. disability/handicap) between subtypes of ischemic stroke, and costs of stroke.

- **Incidence study of vascular disease (stroke, myocardial infarction, and peripheral vascular disease) – estimated to commence in 2007.** This will enable us to:
  - reassess stroke incidence and to determine whether stroke incidence is changing
  - investigate common risk factors between the vascular diseases
  - investigate genetic factors (either as risk factors for stroke, or as factors that influence outcome after stroke).
**Abstracts**

**8.50AM  H. DEWEY  HEALTH ECONOMICS: FROM MODELS TO POLICY**

**Background:** In 1999, an economic model for stroke was commissioned by the National Stroke Foundation as a tool to assist in the Foundation’s advocacy role of informing government policy on stroke. A ‘Model of resource utilisation, costs and outcomes for stroke’ (MORUCOS) was developed collaboratively by the Centre for Health Program Evaluation (CHPE), University of Melbourne and the National Stroke Research Foundation (NSRI). Detailed epidemiological and resource utilisation data collected in the North East Melbourne Stroke Incidence Study (NEMESIS) was incorporated into the model so as to provide a comprehensive overview of the burden of stroke in Australia. The resultant model provides description and projection of stroke incidence and its disease and cost burden, and facilitates the evaluation of stroke interventions intended to reduce its burden. The model provides both prevalence based (annual) and incidence based (lifetime cohort) costs.

**Progress to date:** MORUCOS has been used to describe and project the magnitude and composition of stroke costs in Australia. The model has also been used to examine the cost-effectiveness of several stroke interventions, including the use of aspirin and thrombolysis.

**Future directions:** Our plan is to use MORUCOS as a technical tool to facilitate a systematic comparison of the cost-effectiveness of stroke interventions across the spectrum of care from primary prevention through to acute treatment, secondary prevention, rehabilitation and long-term care. This approach will provide data which will sensibly inform resource allocation for stroke so as to achieve the best value for money spent. This technical approach is readily transferable to other disease areas and is internationally applicable. Our challenge will be to translate our research findings into appropriate action at the state and federal government levels.
Background: In my PhD studies evidence of the prognostic value of the Oxfordshire Community Stroke Project classification was provided. The worse outcome of TACI patients has now been demonstrated to persist out to two years after stroke, and to apply to a wide range of outcomes including mortality, disability, handicap, depression and HRQoL. However, more importantly, depression and anxiety were determinants of handicap and HRQoL, independently of physical impairment and disability.

Future Directions: On the Central Coast we are planning an observational study of mood impairment after stroke. The aims are to determine the prevalence and time-course of mood impairment after stroke, the effects of mood on mortality, vascular events, cognition and HRQoL, and to identify predictors of post-stroke mood impairment. As data is scarce on the efficacy of treatment of post-stroke depression, we plan to follow our observational study with a multicentre randomised controlled trial of antidepressant therapy versus placebo.
Background: Dementia exists post-stroke. What is unclear is the magnitude and nature of the causal relation between stroke and dementia. Currently there is great interest in studying the link between vascular disease and Alzheimer's disease (AD), as some even consider AD to be a primarily driven by a vascular aetiology.

Progress to date: In NEMESIS, the risk of dementia 1 year after a first-ever stroke of mild severity was not raised compared to matched controls, in the absence of aphasia. The results vary from previous hospital-based studies due to methodological differences. However, the risk of cognitive impairment (not amounting to dementia) was clearly greater even among such strokes at 3 and 12 months after stroke.

Future directions: In the existing cohort of NEMESIS, 2-year follow-up analysis is underway to determine longer-term risk of dementia after stroke. Research in this area is plagued by differences of opinion regarding the definition of dementia. Refining cognitive tools for such purposes and bypassing definitional difficulties will be important in future research. Interest currently lies in examining the contributions of risk factors for vascular disease towards cognitive impairment and dementia preferably in population-based cohorts, with cerebral macro-vascular and micro-vascular disease (carotid atherosclerosis, cerebral perfusion, stroke and white matter disease) being intermediates in the causal pathway. Although many cohorts have been established to examine correlates of traditional vascular risk factors for cognition, the use of existing cohorts to look at novel risk factors for cognition (physical activity, obesity) will be explored. Brain imaging will need to play an important role in such research.
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9.50AM C. LEVI ROLLING OUT STROKE UNITS

**Background:** Organised care in an acute or post-acute stroke unit has a significant impact on stroke morbidity and mortality. The absolute risk reductions based on the stroke unit trialist’s meta analysis indicate a number needed to treat of 22 to prevent one death, 14 to prevent one admission to institutional care, and 16 to prevent one person being dependent. 

Approximately 40,000 Australians per annum suffer stroke. Based on extrapolations from the North-East Melbourne Stroke Incidence Study (Gilligan A, Donnan G, personal communication). 83% of stroke presentations would be eligible for stroke unit care. With the absolute reductions in death or dependency applied to incident of cases, over 2000 stroke sufferers could be annually prevented from either death or dependency. This compares to a figure of approximately 600 cases for the intervention of tissue plasminogen activator in the sub 3 hour presentation. The public health impact, therefore, of a roll out of stroke units across the metropolitan and regional areas of Australia would be significant. The National Stroke Strategy survey of access to stroke unit care in the late 1990s suggested that only approximately 20% of stroke sufferers were cared for in organized stroke units. Clearly this is suboptimal and strategies need to be developed and implemented for set-up and roll out of stroke units nationally.

**Progress to date:** In the US, the concept of primary and secondary stroke centres has been developed. The primary centres forming a hub and comprising acute stroke teams with written care protocols and emergency transport and emergency department services, stroke units and neurosurgical support. The National Stroke Unit Programme, in consultation with a broad range of state holders, has developed Australian criteria for levels of stroke services applicable to metropolitan, regional and rural geographies. Around this template the NSW State Government has funded the development or enhancement of 18 stroke units in hospitals receiving 200 or more stroke patients per year within the greater metropolitan area. These units are organized according to a “hub and spoke” models, with an administrative support system and an outcomes evaluation system now in place. A broad evaluation of this initiative is planned in collaboration with the NSRI. The Royal Brisbane Hospital stroke unit is establishing networks for stroke care with regional Queensland similarly using a hub and spoke model.

**Future directions:** Given the local activities occurring within cities and states around the country, there is a clear need to co-ordinate and collaborate in stroke unit development and roll out. With this in mind, the Australasia Stroke Unit Network (ASUN) has been formed to attempt to provide a communication network between clinical leaders in stroke, to address the gap between evidence and reality in stroke care delivery, and to facilitate audit and benchmarking. ASUN will also provide an interdisciplinary pool of stroke experts to review and comment on the now developing national stroke care guidelines. Additional key initiatives will focus attention on the “intersections of care”, particularly community knowledge of stroke warning signs and risk factors, pre-hospital services, emergency department stroke management and post acute stroke care.

Background: Evaluation of health services in delivering optimal care, such as stroke units, rests on determining associations between the structure, process and outcome of care delivery (Donabedian 1988). In addition, appropriate classifications of structure (organisation of care), process (clinical activities) and outcome measures need to demonstrate a plausible link. Both quantitative and qualitative methods are used to ensure that outcomes can be fully explained within the context of perceived health system strengths and limitations. This is important as health services are often dynamic or are in an evolving state. Therefore evaluation methods need to be appropriate in order to describe evaluation findings with the context of the environment in which they have taken place. As an example the formative evaluation of the Stroke Service Model developed as part of the National Stroke Unit Program (National Stroke Foundation) will be given. The model anticipates links with less resourced hospitals to specialised stroke units to increase capacity in the health system to optimally treat stroke. In Australia, access to stroke units is not universal and is influenced by factors that include limited specialist infrastructure and geographical distances. In order to garner support for implementation of stroke units nationally, evidence of what makes stroke units effective over current models of care and identifying models that can overcome barriers unique to Australia are essential. Evaluation of the model has been required to assess a) technical feasibility; b) determine how the model has worked within and between demonstration sites; c) identify the facilitators and impediments to the model; d) describe what modifications are required to ensure effectiveness and generalisability; and e) determine the effectiveness of the model using an appropriate set of process and outcome measures for acute health services.

Progress to date: Qualitative research methods were employed for the initial model field testing. This included the use of an interview schedule that was piloted first at a non-participating site. Interviews were conducted with various health care providers (n=28) who provided overlapping sources of information from 5 sites. Key themes were identified and included health system issues not exclusive to stroke (eg lack of allied health in regional areas), the usefulness of clinical management tools, presence of a clinician leader and project officer, links to specialists, number of stroke patients treated, skill level, availability of resources, executive support and communication. Overall, the model was supported by clinicians and seen to enhance peer support and optimise care across geographical areas.

Future directions: Additional quantitative data to determine the effectiveness of the model (impact on patient care delivery and patient outcomes) will be facilitated through on-going work as part of the NSW Greater Metropolitan Transition Taskforce (GMTT) initiative. Process of care and outcome measures will be obtained. Process data reflects changes in health professional behaviour and attitudes that by implication impact on patient outcome. These are important to collect as the GMTT stroke program is still in the early stages and outcomes relating to the benefits of health system changes will be underestimated, until a sufficient run-in stage has occurred.
**BASIC SCIENCE**

**11.00AM  D.HOWELLS  WHICH OUTCOMES IN ANIMAL MODELS IN STROKE?**

**Background:** There has been a puzzling and frustrating inability to translate the clear animal experimental evidence for neuroprotection in models of stroke into clinical practice. The most parsimonious explanation for this failure is that in some way our initial animal evaluations are inadequate.

**Progress to date:** Whilst the thread occlusion model of stroke is still the “work horse” of our animal studies because of its reproducibility we now also collaborate with the Jarrott group who use the vasoconstrictor peptide endothelin (ET-1) to directly constrict the MCA without traumatic carotid surgery or the need for an potentially neuroprotective anaesthetic agent on board at the time of stroke and are planning to introduce an embolic method to better mimic the vascular events that accompany human stroke. We now also study the effects of hypertension and diabetes in our rats to determine how these common co-morbidities influence the outcome of our trials.

**Future directions:** Traditionally the most common assessments used to evaluate the success or failure of animal stroke experiments have been measures of infarction (TTC stain for active mitochondria or nissl staining to discriminate between dead or normal cells) and simple “neurological scores” applied 24 hours after onset of ischaemia. Recent studies have
suggested that these may not correlate particularly well with similar measures made 1 week later. Also stem cell implantation experiments provide strong evidence that treatments started up to two weeks after stroke can provide improvements in neurological scores comparable with those produced by neuroprotection even though infarct volumes do not change and there is little evidence that stem cells have differentiated or integrated into the host brain. To address these issues we are implementing a program to evaluate the utility of a more rigorous battery of behavioural tests applied at different times out to 1 week after stroke. We are comparing the discriminatory powers of infarct volume assessments in control and neuroprotected animals made at 24 hours with those made at 1 week. We are also determining how well these anatomic and functional measures correlate with MRI measures of infarct growth, final infarct volume and white matter injury determined by DW, T2 and DT imaging.

11.20AM G. LIBERATORE WHO WANTS tPA?

**Background:** Tissue type plasminogen activator (tPA) is a widely used thrombolytic agent that effectively removes blood clots. However, tPA has recently been shown to promote excitotoxic and ischaemic injury within the brain and this has implications for the use of tPA treatment of ischemic stroke. These conclusions are drawn from studies using tPA-/− mice that were shown to be resistant to excitotoxic (kainic acid) induced injury. At lest in this model, the effect of tPA at promoting injury was dependent upon its ability to generate plasmin, since plasminogen -/- mice were also resistant to kainic acid-induced injury. In animal models of Ischemic stroke, t-PA has been shown to be either beneficial or deleterious. These discrepancies are largely explained by the different animal stroke models used: if tPA was administered to reperfuse a vessel with a short time frame after a thrombotic occlusion, tPA was usually found to be of benefit. If on the other hand, the model did not require the reperfusing ability of tPA (i.e. models requiring permeant occlusion of the MCA), then tPA had a negative effect on outcome. The mechanistic basis for the negative effect of tPA is unclear and, at least in the animals stroke models, its effect may be unrelated to its ability to act as a plasminogen activating agent. The use of tPA in the treatment of ischaemic stroke in humans is effective provided treatment is initiated within three hours of stroke onset. Later use has been shown to promote intracerebral haemorrhage and we have speculated that this may be related to the ability of tPA to promote injury if it is allowed to access the CNS. Taken together these findings have promoted the need to develop other thrombolytic agents that do not display detrimental effects within the CNS.

**Progress to date:** On candidate enzyme has been found in the saliva of the blood feeding vampire bat (*Desmodus rotundus*). This protease known as Desmodus rotundus Salivary Plasminogen Activator (DSPA; “Desmoteplase”) is a highly effective plasminogen activator but in contrast to tPA, is nearly inactive in the absence of a fibrin cofactor. We have compared the ability of DSPA and tPA to promote excitotoxin induced neurodegeneration in two different animal models of excitotoxic injury (kainic acid & NMDA induced excitotoxicity). Results of this study indicate that unlike tPA, DSPA does not promote neurotoxicity in vivo.

**Future directions:** Experiments are underway to assess the toxicity of tPA vs Desmoteplase (DSPA) in experimental reperfusion injury following a stroke model (reversible thread occlusion of the middle cerebral artery in rats).
11.40AM  N. SPRATT  DOES FMISO IMAGE THE PENUMBRA?

**Background:**  Salvage of the ischemic penumbra has been the major goal of acute stroke treatment. Reliably identifying the penumbra remains problematic with available techniques. $^{18}$F-fluoromisonidazole ($^{18}$F-FMISO), a PET marker of hypoxic cells, has shown promise imaging the ischaemic penumbra in human studies. The pattern of binding, timing, and correlation with clinical improvement all suggest binding to the penumbra. The essential component yet to be demonstrated is that FMISO-bound tissue is destined to infarction without intervention, yet remains potentially salvageable.

**Progress to date:** Earlier work in our laboratory has examined the pattern of binding of $^{18}$F-FMISO in a rat 2-hour middle cerebral artery thread-occlusion model, and showed a pattern of binding mimicking that in human studies. Binding initially was in the entire ischaemic territory, surrounded the infarct core at later stages, and by 24 hours there was negligible binding. The tritiated form of the probe ($^{3}$H-FMISO) has been evaluated, and provides better resolution in animal autoradiographic studies. It also enables liquid emulsion autoradiography, whereby the binding pattern and histology can be examined at the same time on the same tissue sections.

**Future directions:** The major aim of this project is to establish that FMISO does image the penumbra. This will be achieved by demonstrating that FMISO-bound tissues are salvageable if reperfused early after FMISO injection, but are destined to infarction if not reperfused. Two cohorts of animals will be used. Both will receive $^{3}$H-FMISO 10 minutes
after the induction of MCA occlusion, and be sacrificed for autoradiography and histology after 24 hours. In the first cohort reperfusion will be performed soon after \(^3\)H-FMISO injection. In the second cohort MCA occlusion will be permanent. Liquid emulsion autoradiography will allow study of the cellular pattern of binding, and enable us to determine whether certain cell types are more prone hypoxia, or infarction.

Preliminary work is underway to determine the minimum time needed between tracer injection and reperfusion and the feasibility of delaying imaging by 24 hours after the injection of tracer.

**Background:** Drug discovery and development is a lengthy process and the chances of a drug candidate having desirable pharmacokinetic and toxicological attributes are not high. Thus the process can take at least five years and at a cost of $20 million before a drug is ready for Phase 1 to 3 trials to establish it is a clinically effective as a neuroprotectant drug that minimizes the disability after acute stroke. A strategy to speed up the development process is to use a drug or a naturally occurring substance that is known to be safe for human use.

**Progress to date:** At the First Annual Stroke Research Retreat, I proposed that Epogen and Minocycline were existing parenteral drugs that, on the basis of neuroprotection in rodent...
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models of focal stroke, could be used in Phase 1 and 2 studies to establish if they are clinically effective as neuroprotectants.

Recently, rodent studies of focal cerebral ischaemia have shown that a combination of two widely used natural products, caffeine and ethanol were effective neuroprotectants at clinically relevant doses (Aronowski et al (2003) Stroke 34: 1246-51). Interestingly, this effect was only seen as a combination (“caffeinol”) and not when given alone. A pilot Phase 1 study in stroke patients has established that caffeine can be given safely at a dose of 8 mg/kg and ethanol at a dose of 0.4 g/kg by intravenous infusion and can also be combined with Alteplase (Piriyawat et al (2003) Stroke 34: 1242-45).


Future directions: The ‘caffeinol’ combination has reached the stage where Phase 2 trials are warranted but it is unlikely that the pharmaceutical industry would sponsor a trial as this combination could not be patented. Thus it would be necessary to have organizations such as The Wellcome Trust and NIH fund such studies.

Further research needs to be done in animal models of stroke to establish the dosage regimen for Activated Protein C and vitamin K before clinical trials can progress.

12.20PM  V. O’COLLINS  TWINS, BUT WHICH ONE?

Background: Clinical trials to date suggest that many if not most drugs do not affect the outcome of stroke patients. However, it may be a case of too little, too late. The Time Windows in Neuroprotection study (TWIN) aims to deliver a combination of drugs in a timely manner after the onset of ischemic or haemorrhagic stroke. The hallmarks of this study include measures to bridge the gap between laboratory and clinical work, together with a methodology for objective, evidence-based drug selection. In particular, the choice of drugs will be based on a review, rating and expert panel assessment of the 1000+ putative neuroprotectives identified in the scientific literature. The most promising agents will go on to be tested in appropriately aged and diseased animals, using quality standards imported from clinical trial methodology. The clinical protocol requires delivery of the most compatible combination by ambulance officers or intensive care units within 3 hours of stroke onset. At first instance, the trial is a collaboration between Austin Health, Royal Melbourne Hospital & Metropolitan Ambulance Service. The narrow time window in this trial parallels those successfully used in animal studies and should increase the possibility of an efficacious and safe outcome for patients.

Progress to date: Preliminary review of neuroprotective studies for purposes of drug selection completed. Preparation for initial trials of neuroprotective agents in the rat model of focal cerebral ischemia commenced. Clinical trial not yet commenced.

Future directions: Top ranking drugs from the neuroprotectives review will be presented to an expert panel (blind to drug identity) to be evaluated against six criteria (1) efficacy in experimental models of stroke; (2) stability and compatibility; (3) safety; (4) availability and cost; (5) pharmacokinetic and pharmacodynamic properties; and (6) putative mode of action. Drugs selected by the panel will be tested individually in the rat model of temporary MCA occlusion and the best three as determined by in vivo studies will be tested in combination at
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0, 3, 6 and 12 hours post occlusion. Measures of efficacy using individual drugs will be contrasted with outcomes predicted mathematically by neural nets trained using historical data gathered during the review process. Animal studies will be preceded by initial assessment of the impact of rat age on outcome in order to determine “how old is old” in the rat model of stroke.
Background: Human cerebral tissue cannot survive an episode of complete ischaemia for more than a few minutes. Penumbral tissue is incompletely ischaemic, electrically and functionally silent but without evidence of infarction. Imaging the penumbra in humans requires minimally invasive tools that are not dependent upon a histological endpoint, and many imaging tools are now available that may fulfil these requirements. $^{15}$O-PET was the earliest, and most thoroughly validated technique, giving thresholds which allow prediction tissue fate. It is time consuming, invasive, and uses radiation, but no other imaging tool has been developed to this point. Only MRI offers perfusion and metabolic indices in clinical practice for assessing and managing human stroke.

Progress to date: We attempted to use $^{15}$O-PET to assess the reliability of quantitative methods for the calculation of CBF using perfusion MRI. Fourteen healthy elderly volunteers have been imaged in rapid succession with diffusion and perfusion MRI, then $^{15}$O-PET CBF and CMRO$_2$/OEF studies. MRI quantitative CBF was determined using automated algorithms for the detection of an arterial input function. We were unable to identify a reliable method for MRI perfusion quantification.

Future directions: To improve reliability of perfusion MRI as a step toward it assuming a role as the gold standard for the assessment of the ischaemic penumbra will require the ability to sample the arterial input function at higher resolution, but without image distortion.
Background: Most therapies in acute stroke are aimed at rescuing penumbral tissue that is threatened by necrosis prior to irreversible injury occurring. It is likely that both the volume and spatial location of the ischemic penumbra will determine the functional benefit associated with its salvage. We have used positron emission tomography with the ligand, $^{18}$F-Fluoromisonidazole, a 2-nitroimidazole derivative that identifies hypoperfused tissue that is severely hypoxic but metabolically viable to identify putative penumbral tissue in a large series of consecutive patients presenting with ischemic and hemorrhagic stroke. Spatial transformation of all data sets into stereotactic coordinate space allowed mapping of hypoxic tissue relative to the infarct and enabled comparison between patients with heterogenous infarcts. Such maps ('Penumbragram's) were used to study the change in spatial distribution of the penumbra with time since ischemic stroke onset. Longitudinal clinical assessments at the time of PET study repeated at 1 week, 1 month and 3 months after onset of stroke were used to assess the fate and functional impact of spontaneous hypoxic tissue survival. Finally this method was applied to patients presenting after intracerebral haemorrhage to determine whether tissue with characteristics of the penumbra occurs in the perihematoma region.

Progress to date: After ischemic stroke infarct expansion occurs from the centre to the periphery of the ischemic region at the expense of penumbral tissue. The fate of hypoxic tissue is not pre-determined. The volume and the prevalence of patients with hypoxic tissue declined with time. Hypoxic tissue was observed as late as 47 hours after stroke onset. Spontaneous survival of hypoxic tissue was associated with functional improvement at 1 week which was sustained at 3 months. This association was strongest in those studied within 12 hours of ischemic stroke but the presence of a benefit even in those studied later suggests that hypoxic tissue that underwent infarction may be an important target for therapeutic intervention. In contrast after ICH only small volumes of hypoxic tissue was observed in association with larger hematoma volumes.

Future directions: This technique can be used to determine differences in the characteristics of the penumbra occurring in white matter and grey matter. This technique can also be to determine the metabolic characteristics of regions identified on the basis of abnormality on diffusion and perfusion MRI in patients after ischemic stroke.
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9.40 AM  K. BUTCHER  EDEMA EXPANSION IN CEREBRAL HEMORRHAGE IS UNRELATED TO TRANSIENT HYPOPERFUSION

Background: The mechanisms of peri-hematomal injury in primary intracerebral haemorrhage (ICH) are incompletely understood. Rational acute medical therapies require elucidation of the nature and effects of blood flow changes following ICH.

Progress to date:

Methods: Blood flow changes and peri-hematomal edema were studied serially with perfusion (PWI) and diffusion weighted MRI (DWI). Acute and sub-acute PWI and DWI studies were performed prospectively in 21 patients presenting with ICH.

Results: Mean patient age was 64.2 years (45-89) and average baseline NIH stroke scale score was 12.2 (3-24). The median times to initial MRI and sub-acute scans were 20.5 h and 5 d respectively. Initial CT scan demonstrated an average hematoma volume of 26.1 (4-84) mL. Hematoma volumes were consistently larger on T2* (mean 55.1 mL) and T2-weighted (mean 35.8 mL) MRI scans. Co-registration of CT and MRI images confirmed PWI and DWI abnormalities were outside the visible hematoma. Acute peri-hematomal mean transit time (MTT) was significantly correlated to hematoma volume (R=0.6, p≤0.004). Significant peri-hematomal MTT delay was seen only in patients with hematoma volume >15 mL (mean MTT delay = 4.6±2.8s). All blood flow changes resolved completely on the sub-acute PWI studies. Peri-hematomal edema on T2-weighted sequences was present in all patients. Apparent diffusion coefficient (ADC) values within this region (1178±213 x10^-6 mm²/s) were increased 29% relative to contralateral homologous regions. There was a strong correlation between relative edema volume (=absolute edema volume/hematoma volume) and ADC (R=0.62, p≤0.003). Absolute edema volumes increased by 35±41 % on sub-acute scans, but the positive correlation between ADC values and relative edema volume persisted (R=0.79, p≤0.002). Conclusions: Cerebral perfusion appears to be transiently decreased in a limited peri-hematomal region, in large hematomas, but this is not associated with restricted diffusion. Therefore the decreased blood flow does not appear to result in ischemia. The strong correlation between increased water diffusivity and relative edema volume is most consistent with a vasogenic etiology.

Future directions: This work indicates that ischemia is not a major part of the pathology of peri-hematomal secondary injury. What is not known, is whether reducing blood pressure acutely will actually cause ischemia. Similarly, it remains to be proven that reducing blood
pressure acutely will have any effect on hematoma or edema evolution. Therefore, an acute blood pressure lowering trial is required. In addition, this trial would benefit from imaging endpoints, such as those presented here.

10.00AM M. WALSH
MRI AND STROKE: WHAT IS AFTER DIFFUSION/PERFUSION?

Background: We have been performing high density EEG together with perfusion and diffusion MRI in acute stroke patients at the Royal Brisbane Hospital, Queensland.

Progress to date: High density EEG has been evaluated as a surrogate and complementary marker to MRI in 10 acute stroke patients with middle cerebral artery stroke in the previous 12 months. We hypothesized that the EEG would correlate with NIHSS scores during and following admission. We found that in this small group changes in delta power over the lesion in the initial 48 hours were equivalent to MRI perfusion and diffusion data in predicting outcome from stroke.

Future directions: Because of the limitations of diffusion and perfusion imaging in stroke patient evaluation we have designed and are currently manufacturing a novel MRI head coil for Sodium imaging. Sodium has been shown to increase significantly in cells following ischemic insult and may act as a “tissue clock” for stroke patients. It is envisaged that a dual coil will be available by end 2003.
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10.20AM R. MULLIGAN NEW PET LLIGANDS IN STROKE

Background: Ischemia induced cell death by both necrosis and apoptosis leads to neuronal damage following acute stroke. There is increasing evidence to suggest that apoptosis may be responsible for the more gradual loss of neurons in the region outside the stroke’s core. An in vivo marker for the detection of apoptosis in humans would provide vital information for assessing neuroprotectant therapies.

Apoptotic cells initiate a form of suicide where nuclear and cytoplasmic condensation results in autodigestion of cell components. A number of intracellular events can lead a cell to commit to apoptosis. However, they all converge towards a common intracellular pathway involving the activation of caspases, a family of cysteine proteases with aspartyl protease activity. Caspase activation occurs prior to any morphological changes in the cellular ultrastructure and has a role in mediating many morphological and biochemical events in the apoptotic cell. Effector caspase activation appears to be an irreversible commitment to cell death. Radiotracers for imaging apoptosis are limited. At the Austin PET Centre we are in the process of developing novel non-peptide radioligands for apoptosis that bind specifically to effector caspases. Such radioligands should provide a marker for cells committed to programmed cell death.

Progress to date: Three groups of small molecule caspase inhibitors have appeared in the literature over the last 2 years. As a proof of concept for the use of caspase inhibitors to image apoptosis we have chosen three 5-nitro-isatins which should inhibit apoptosis at
micromolar concentrations as our prime target compounds for the development of PET radiotracers. Initially we will concentrate on developing fluorine-18 ($t_{1/2}=108\text{min}$) labelled compounds to maximize the \textit{in vivo} pharmacokinetic data obtained from the scan. A standard for one of these compounds (the ethylfluoro isatin) has been synthesised. Synthesis of the radiolabelling agent required for the radiofluorination has been achieved for the first time at the PET Centre, viable methods of analysis have been developed and the investigation of optimal labelling conditions is underway.

\textbf{Future directions:} Published data suggests that the ethylfluoro isatin will show affinity for caspase 3. This will be tested by screening for caspase 3 inhibition in an \textit{in vitro} assay using recombinant human caspase 3. \textit{In vivo} pharmacokinetics will then be assessed using a validated middle cerebral artery occlusion animal model already established at the National Stroke Research Institute. Synthesis of the tritiated compound will enable dual injection of the $^{18}\text{F}$- and $^{3}\text{H}$-labelled compound and enable additional information to be obtained on the exact site of binding and identify how effectively the radiotracers are targeting apoptotic cells.

The search for caspase inhibitors with nanomolar affinity for effector caspases that are desirable candidates for labelling with positron emitters will continue in case initial studies indicate that number of apoptotic cells in stroke is too low to image with compounds that inhibit apoptosis at micromolar concentrations.
**Background:** There have been numerous trials of neuroprotection in patients with acute ischaemic stroke without any evidence of benefit. This is in spite of quite strong evidence of significant volume reductions and improvement in clinical outcomes in animal models of focal cerebral ischaemia. The reasons for this failure of translational research are protean and need to be considered seriously if progress is to be made. One such approach is to ensure adequate time windows, that is using the thrombolytic 3 hour window as a paradigm. This may mean giving therapy in ambulances since most neuroprotectants are relatively safe.

**Progress to date:** We have developed a protocol for the Time Window in Neuroprotection (TWIN) Study in which combination neuroprotection therapy will be given in the ambulance and outcomes assessed at 3 months. The compounds used will be derived from the objective review of the literature and the need to utilise a sequential approach to arrest of the ischaemic cascade. It is proposed to pilot this protocol as a phase II study to assess safety and feasibility.

**Future directions:** If the pilot study is successful, funding will be sought to expand TWIN into a phase III, multicentred study. Other neuroprotectants such as cooling with intravenous therapy could also be considered.
Background: Standards and expectations from experimental stroke fall far short of those required from human studies. This is one of a small number of plausible explanations for the failure of human trials to confirm clinical efficacy for drugs shown to be neuroprotective in animal models of stroke.

Progress to date: A meta-analysis of the efficacy of nicotinamide in experimental stroke has been performed. Study quality was, by clinical trial standards, poor. High quality studies gave a more precise estimate of the overall treatment effect than low quality studies. Studies published in abstract only gave a lower estimate of effect size than those published in full, suggesting the existence of a publication bias in favour of positive studies. The overall effect of nicotinamide, on infarct volume, neurological score, or a combined score, was highly significant (28.7% improvement in outcome, 95% confidence interval 22.7 to 34.7%, \(p<10^{-15}\)). Nicotinamide was protective at doses of 100 to 750mg/kg and when given between 1 and 6 hours after the onset of ischaemia. Aspects of study design impacted on the estimate of outcome. Nicotinamide was less effective in animals with diabetes or hypertension than it was in healthy animals; in permanent versus focal ischaemia; and when given intraperitoneally rather than intravenously. There was a non-significant over-statement of efficacy in animals who received ketamine anaesthesia.

Future directions: Other candidate neuroprotective drugs are being subjected to the same rigorous analysis. The in-use characteristics of these drugs may provide the basis for a more coherent classification of neuroprotective drugs. Other approaches to the lack of efficacy in human studies, including the use of reverse transgenics in observational studies of stroke outcome to explore human stroke pathophysiology, are currently being considered.
Background: It is now well established that treatment in acute stroke units results in fewer deaths and lower levels of dependency. However, it is unclear whether the effectiveness of stroke units is due to particular components of care or to the total package. One way stroke unit care may prevent death and reduce disability is through more aggressive detection and treatment of secondary complications of stroke. Although the contribution of immobility to complications and death is difficult to quantify, there is evidence that patients managed in a stroke unit promoting early, active rehabilitation had fewer deaths and better outcome than patients managed in general medical wards without early mobilisation. Our aim is to conduct the first randomised controlled trial of very early rehabilitation.

Progress to date: In Phase 1 we examined physical activity levels, location of activity and person(s) assisting with activity in 5 acute stroke units in Melbourne. Behavioural mapping techniques were used and we recruited 64 patients to this study. The results of this work have been presented at the Stroke Society of Australasia National Congress and the European Stroke Congress. We are currently completing the work up for Phase 2 (Pilot RCT) which we aim to commence in February 2004.

Future directions: Phase 3 (multi-centre RCT) is planned to commence in 2006.
Background: Acute post-stroke hyperglycaemia has been associated with larger infarct volumes and greater stroke severity, regardless of diabetic status. Post-stroke hyperglycaemia has been attributed to activation of the hypothalamic-pituitary-adrenal axis but never a specific cortical location. The insular cortex (IC), a site with autonomic connectivity, is a potential mediator of neuroendocrine dysfunction in stroke. We hypothesized that acute ischemia of the IC is associated with admission hyperglycaemia.

Progress to date: Acute DWI, admission plasma glucose, and HbA1c levels were obtained in 31 patients within 24 hours of ischemic stroke onset. Acute DWI lesion volume was calculated using planimetric techniques and involvement of the IC was determined. **Results:** Patients with acute DWI lesions involving the IC had higher admission glucose levels (9.5 ± 3.6 mmol/L) compared to those without IC involvement (6.7 ± 2.1 mmol/L, p=0.01). A multivariate linear regression model including lesion location in the IC, DWI lesion volume and history of diabetes mellitus showed that IC involvement was a significant independent predictor of acute glucose level (p=0.001). When controlling for the effect of IC involvement, acute DWI lesion volume was not associated with higher glucose levels (p=0.849). Pre-existing diabetes was independently associated with higher acute glucose levels (p=0.008). There was no significant association between HbA1c and acute glucose level (p=0.737). **Conclusion:** Acute bioenergetic compromise in the insular cortex contributes to post-stroke hyperglycaemia, independent of acute DWI lesion volume. This may represent acute neuroendocrine dysregulation (stress response) mediated by IC injury. This novel finding has implications for future studies of hyperglycaemia and stroke prognosis.

Future directions: Hyperglycaemia and haematological abnormalities in acute ischaemic stroke: Prospective assessment of impaired fibrinolysis (elevated PAI-1 and depressed t-PA levels) in diabetic and hyperglycaemic non-diabetic acute stroke patients; we aim to quantify and correlate the state of hypofibrinolysis in hyperglycaemic stroke patients with clinical and imaging outcomes (final infarct volume and infarct expansion on EPI MRI).
Background: EPITHET is a multicentre acute stroke trial, which aims to determine whether perfusion-diffusion MRI can be used to identify responders to rt-PA beyond 3 hours. The historically randomised, pilot EPITHET study* indicated that PWI > DWI mismatch predicted benefit from rt-PA. EPITHET is a prospective, randomised controlled trial and is being conducted to confirm this hypothesis. A second hypothesis is that the risk of hemorrhagic conversion will be higher with large DWI lesions.

EPITHET is a double-blind, randomized (1:1) trial of rt-PA versus placebo in 100 patients with hemispheric infarction 3-6 hours after stroke onset. The study currently involves 11 centres in Australia and 1 in New Zealand. Patients have standardised DWI, PWI and MRA sequences performed prior to treatment. The imaging protocol is repeated 3-5 days post-treatment to measure any expansion of the infarct core (DWI volume) and contraction of the PWI lesion, providing a measure of reperfusion. The DWI scans are evaluated for the presence and degree of any hemorrhagic transformation. The MRA is repeated to determine whether or not recanalisation has occurred in those with MCA stem or major branch occlusion. The final infarct volume (T2-WI) is measured (cm$^3$) at 90 days. The presence of symptomatic hemorrhagic transformation is graded by volume (cm$^3$) of hemorrhagic tissue on MRI (day 3-5). Correlations will be made between the acute DWI volume and any symptomatic hemorrhagic transformation.

Progress to date: To date, 27 patients have been enrolled in 6 centres. This is the only randomised, placebo-controlled trial to determine whether t-PA attenuates infarct growth on MRI beyond 3 hours. There is a non-randomised study using open label rt-PA 3-6 hours in the USA called DEFUSE to determine MRI prognostic factors. The DIAS trial is using the thrombolytic agent, desmopressin 3-9 hours after stroke onset, to determine optimal dosage, safety and potential efficacy signals in ischemic stroke.

Future directions: EPITHET is a classical, investigator-driven study that will test crucial hypotheses, specifically whether the benefits and risks of thrombolysis can be individualised using PWI and DWI in the 3-6 hour time window. It is also one of the few proof of concept MRI-based trials.

EPITHET Trial

- 13 centres Australia, New Zealand
- NINDS criteria, but 3-6 hours post-onset
- 100 patients, tPA vs placebo, after baseline CT, MRI (PWI, DWI, MRA)
- Repeat MRI day 3, day 90
- Clinical follow-up mRS, Barthel Index
- 28 patients randomised to September 2003
NAME: DR ANNE L. ABBOTT

Position and Institution: Research Fellow, NSRI

Contact details: via 03 9496 2888

Qualifications: MBBS FRACP

Research Experience: Completing a PhD in the field of carotid disease and identification of high risk patients using transcranial Doppler embolic signal detection. Have also published on the diagnosis of systemic necrotising vasculitis

Relevant Publications:

NAME: MS VIRGINIA ALDRIDGE

Position and Institution  Acting Nurse Unit Manager,
Ward 7BAustin Health

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9496 5414
Mobile: 0402 149 165
Email: virginia.aldridge@austin.org.au

Qualifications: Post Graduate Certificate in Nursing (Neuroscience) RMIT University, 2000
Bachelor of Nursing(pre-registration) RMIT University,1998

Current Research Interest: Clinical research at a ward level.
NAME: DR LOUISE ALLPORT

Position and Institution: Stroke Fellow, The Royal Melbourne Hospital

Contact details: (03) 9342 8448, louise.allport@mh.org.au

Qualifications: FRACP (Nov ’03)

Research Experience: First year as research fellow

Current research interest:
1. Hyperglycaemia and Stroke
2. Coagulopathy (impaired fibrinolysis) in the hyperglycaemic stroke patient.

Relevant publications: Nil yet

NAME: MRS TESS ANDRIGHETTI

Position and Institution: Clinical Trials Co-ordinator NSRI

Contact details: 9496-2581, e-mail: tmcqueen@austin.unimelb.edu.au

Qualifications: Registered Nurse
Bachelor of Science (Nursing)
Post Grad Cert (Critical Care)
Post Grad Dip (midwifery), (Infectious Diseases /Epidemiology)

Research Experience: >3 yrs in current position
Public Health education
Conducting research projects for a private medical organisation

Current research interest: Secondary Prevention of Stroke

Relevant publications: Nil
NAME:  MS ETTIE BEN-SHABAT

Position and Institution:  Research Fellow  
National Stroke Research Institute

Contact details:   ebshabat@austin.unimelb.edu.au  
E.Ben-Shabat@latrobe.edu.au  
0422 – 066 678, AH: 9388 9175  
9479 5836 (Mondays and Thursdays)

Qualifications:  Master in Physiotherapy (Neurological physiotherapy)  
Bachelor of Applied Science in Physiotherapy

Research Experience:  
1.  Head injury and parkinsonism (a case study).  
2.  The reliability of isoinertic machine for trunk flexion and extension. (a reliability study).

Current research interest:  
fMRI study of spontaneous and training induced sensory recover after stroke.

Relevant publications:  Not applicable.

NAME:  DR JULIE BERNHARDT

Position and Institution:  Research Fellow, National Stroke Research Institute

Contact details:  
Level 1, Neurosciences Building, Heidelberg Repatriation Hospital,  
300 Waterdale Rd, Heidelberg Heights, 3081  
Phone 9496 2783  
Fax 9496 2650  
Email  Jbernhardt@austin.unimelb.edu.au

Qualifications:  PhD, PG Dip Research Methods, BSc (physiotherapy)

Research Experience:  (1988 – current)  

Current research interest:  
AVERT Phase 2 – pilot RCT of very early rehabilitation after stroke.
Curricula Vitae

**Relevant publications:**
1. Bernhardt J, Dewey H, Thrift A, Donnan G. Inactive and alone: Physical activity within the first 14 days of acute stroke unit care. (submitted)

**NAME:** DR AMY BRODTMANN

**Position and Institution:** Research Fellow, NSRI

**Contact details:** amyb@alphalink.com.au, 0417 569 803

**Qualifications:** MBBS, FRACP

**Research Experience:** Currently completing PhD

**Current research interest:** Cognitive and behavioural problems following stroke, functional neuroimaging

**Relevant publications:**

**NAME:** DR KEN BUTCHER

**Position and Institution:** Consultant Neurologist, Royal Melbourne Hospital

**Contact details:** Kenneth.butcher@mh.org.au

**Qualifications:** BSc, MD, PhD, FRCP(C)

**Research Experience:** Post-doctoral Fellow 2001-2003, Royal Melbourne Hospital: Stroke and MRI. PhD Student University of Western Ontario 1990-95: Autonomic sequelae of stroke and the insular cortex.

**Current research interests:** Stroke Thrombolysis, MRI signatures in acute cerebral ischemia, Primary intracerebral haemorrhage.
Curricula Vitae

Relevant publications:

NAME: MS DOMINIQUE CADILHAC

Position and Institution: Manager Public Health Division
National Stroke Research Institute

Contact details: cadilhac@austin.unimelb.edu.au, (03) 9496 2078, 0403 253 912

Qualifications: MPubHlth, BNurs

Research Experience: Since 1994, I have worked in research environments (Royal Melbourne Hospital and the NSRI). Between 1994 and 1998, I coordinated investigator driven and pharmaceutical company clinical trials in both acute stroke and secondary prevention therapies. Since 1998, I have been an active researcher mainly focused on health services projects. Stroke Care Outcomes Providing Effective Services (SCOPES) has been a principal research study for which I was directly responsible. The study involved 512 stroke participants from nine hospitals and 220 carers. This research was geared to assist in planning stroke services for the Victorian Government and has been presented at both international and national scientific/ public health meetings. Current research studies include the SCOPES II project, a follow-up study of the SCOPES cohort at 3 years for stroke survivors and their carers as well as assessing the prevalence of sleep disordered breathing in this population. In addition, I have conducted the National Stroke Units Program evaluation, to assess the implementation of an integrated model of service delivery to increase access to stroke unit care across Australia, for the Commonwealth Government. I am an associate investigator for an ARC linkages grant (Coping in the face of life adversity. A model of resilience for stroke survivors) and a NHMRC ‘Systems of Care for Chronic Disease’ grant (Evaluation of a multi-disciplinary collaborative care model for vascular disease).

Current Research Interest
- Health systems research related to models of care for the management of stroke
- Prevalence of sleep disordered breathing in chronic stroke survivors
- Long-term outcome of stroke survivors and their informal carers
Curricula Vitae

Relevant Publications:

Government Reports:

NAME: DR LEEANNE CAREY

Position and institution: Senior Research Fellow, 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 La Trobe 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. Postgraduate coordinator, School of Occupational Therapy, LaTrobe University.


Relevant publications:
Curricula Vitae


NAME: **A/PROF BRIAN CHAMBERS**

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

**Contact Details:** National Stroke Research Institute, E-mail: brc@bigpond.net.au

**Qualifications:** MBBS, MD, FRACP


**Current Research Interest:** Australian Urokinase Study (AUST) Steering Committee, Dextran in Carotid Endarterectomy (DICE) Steering Committee, ARCH Steering Committee. Principal Investigator Asymptomatic Stenosis Embolus Detection (ASED) Study and Tirofiban in Acute Stroke Study.

**Relevant Publications:**

NAME: MS SUSAN COX

Position and Institution: Research Assistant, Department of Medicine, University of Melbourne, Austin & Repatriation Medical Centre and National Stroke Research Institute

Contact details: ph (03) 9496 5635
e-mail: susancox2000@hotmail.com

Qualifications: MSc(hons)


Current research interest: (2002-ongoing) Working as part of the Stroke Research Team in David Howells laboratory. Investigating the neuroprotective effects of novel compounds on transient ischemic injury in a rat model of stroke.


NAME: PROFESSOR STEPHEN DAVIS

Position and Institution: Director and Professor of Neurology, The Royal Melbourne Hospital / University of Melbourne

Contact details: Tel: 03 9342 8448.
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E-mail: stephen.davis@mh.org.au

Qualifications: MB BS (University of Melbourne) 1972
MD (University of Melbourne) 1985
FRACP 1980
FRCP (Edinburgh) 2002

Research Experience:

Current research interest:
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: DR HELEN DEWEY

Position and Institution: Senior Research Fellow, NSRI

Contact details: Phone: 9496-2838; Email: helend@austin.unimelb.edu.au

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


Current research interest: Long term outcomes following stroke; assessment of the cost-effectiveness of stroke interventions; early rehabilitation after stroke

Relevant publications:

NAME: PROFESSOR GEOFFREY DONNAN

Position: Director

Institution: National Stroke Research Institute

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

Qualifications: MBBS, MD, FRACP, FRCP (Edin)

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:  MR JOHN FERNANDEZ

Position and Institution:  Research Assistant, Department of Medicine, University of Melbourne, Austin & Repatriation Medical Centre and National Stroke Research Institute

Contact details:  ph (03) 94965635 email jfern@unimelb.edu.au

Qualifications:  MSc(hons)


Current research interest:  (2003-ongoing) Working as part of the Stroke Research Team in David Howells laboratory. Investigating the neuroprotective effects of novel compounds on transient ischemic injury in a rat model of stroke.

Relevant publications:

NAME:  DR AMANDA GILLIGAN

Position and Institution:  Stroke Research Fellow, NSRI

Contact details:  03 94962888
gilligan@austin.unimelb.edu.au

Qualifications:  MBBS (Hons), BSc FRACP

Research Experience:  Currently completing my PhD assessing factors that influence hospital arrival following acute stroke as part of the North east Melbourne Stroke Incidence Study (NEMESIS). In 1992, was the clinical co-ordinator of the Australian Streptokinase Trial (ASK), assessing the efficacy of intravenous streptokinase in acute ischaemic stroke.

Current research interest:  acute stroke treatments

Relevant publications:


**Book chapters**


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**NAME:**  **DR (SYLVIA) JIE GONG**

**Position and Institution:** Research Fellow, NeuroImaging Laboratory, Department of Neurology, Department of Medicine, University of Melbourne, ARMC, Northern Health

**Contact details:** Tel: 9496-3114 (Austin); 9442-2200 (Home); 0424-259-307 (Mobile) E-mail: sgong@unimelb.edu.au

**Qualifications:** PhD, BEng

**Research Experience:**
Research Fellow, Neuroimaging Lab, Austin & Repatriation Medical Centre
Senior Research Associate, Department of Radiology, Cabrini Private Hospital
PhD by Research, Cardiac Investigation Unit, St. Vincent’s Hospital & LTU

**Current research interest:**
Neurological signal and image processing
Diagnostic imaging technology & instrumentation
Biomedical application of pattern recognition & computational intelligence

**Relevant publications (no more than 10)**


NAME: DR DAVID HOWELLS

Position and Institution: Associate Director and Head of Basic Science Division, NSRI, NHMRC Senior Research Fellow, Department of Medicine, University of Melbourne

Contact details: Tel: +61 3 9496 3789
Email: david.howells@unimelb.edu.au

Qualifications: Ph.D.

Research Experience:
Published 58 peer reviewed articles including articles in the New England Journal of Medicine, Lancet, American Journal of Human Genetics and Journal of Neuroscience on topics including the biochemistry and molecular biology of inherited defects of dopamine and serotonin metabolism, macrophage function in CNS infection, the role macrophages and microglia in axonal regeneration, the role of neurotrophic factors in dopaminergic function in animal and human Parkinsonism, and the discovery of a new population of dopaminergic neurons in the Parkinson’s disease striatum. Since 1990, supervised 3 honours students (two 1st class honours) and 5 Ph.D. students of whom 2 have received prestigious awards (Queens Trust award and Young Investigator award 1997 Australian Association of Neurologists, inaugural Sir Gustav Nossel Prize, "Istvan Tork Student Oral Prize" 1999 Australian Neuroscience Society Meeting). Chairman of the organising committee for the 2004 Australian Neuroscience Society Conference in Melbourne. Continuous NHMRC support from 1996 to 2007 with appointment to Senior Research Fellow (NHMRC) in 2001 and award of a program grant from 2003 to 2007. Total grant support since 1990 = $6.4 million.

Current research interests: Mechanisms of neuroprotection and neuroregeneration in models of stroke and spinal injury. Regulation of the destructive and reparative properties of macrophages and microglia after CNS injury. Induction of the dopaminergic phenotype in neurons in the Parkinson’s disease striatum.

Relevant publications:
1. Howells D. Stem cells: do they replace or stimulate? Stroke. 2003;34:2082-2083


NAME: MS LOUISE JAMES

Position and Institution: Stroke Care Coordinator
Acute Stroke Care Unit-Austin Hospital
(Austin Health)

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Phone: (03) 9496 5598 or Pager 5598 via switch (03) 9496 5000, Fax: (03) 9496 3383

Qualifications: Graduate Certificate in Neuroscience’s- 1999
Registered Nurse-Grade 3: Associate Nurse Unit Manager prior to Stroke Care Coordinator Role.

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

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

Relevant publications: Nil

NAME: PROFESSOR BEVYN JARROTT

Position and Institution: Professorial Fellow, Howard Florey Institute of Experimental Physiology and Medicine, Parkville, Vic 3010

Contact details: Email: b.jarrott@hfi.unimelb.edu.au; Ph 8344 1956; Fax 9348 1707

Qualifications: PhD (Cambridge 1969), BPharm (Qld 1965)
Curricula Vitae

Research Experience: 35 years experience in biochemical and neuropharmacology using animal models of neurological diseases such as cerebral ischaemia, epilepsy and essential hypertension

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: MS ROSLYN KELLY

Position and Institution: Clinical Trials Coordinator, NSRI

Contact details: (03)9496 2607 / 0409 425 478

Qualifications: Bachelor of Nursing
Post-Graduate Cert. in Critical Care – Neuroscience.

Research Experience: Working as a clinical trials coordinator at NSRI for past five months in stroke clinical trials. Studied research methods in post-graduate.

Current research interest: Clinical trials - Stroke

Relevant publications: N/A
NAME: DR MASATOSHI KOGA

Position and Institution: Research Fellow, Neuroimaging Unit, National Stroke Research Institute, Austin and Repatriation Medical Centre

Contact Detail: Email: kogamd@aol.com
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Mobile phone: 0409183524

Qualifications: M.D., Ph.D.

Research experience: Ultrasound, Clinical Stroke Research

Current research interest: Cerebral Ischaemic penumbra

Relevant publications:
NAME:  
Dr Erin Lalor

Position and Institution:  
Chief Executive Officer  
National Stroke Foundation

Contact: 
Ph 9670 1000; email: erin@strokefoundation.com.au

Qualifications 
BSci (Speech and Hearing) (Hons): Curtin University of Technology, 1991  
PhD: University of Western Australia, 1996

Research Experience:
PhD investigated language organisation in bilingual Italian-English speakers and its impact on language recovery post-stroke in bilingual aphasia. As a clinician I worked in acute settings investigating the incidence of aphasia post stroke, acute interventions and their effectiveness. I also undertook work looking at long term consequences of aphasia on levels of depression and social isolation and appropriate interventions to reduce psychosocial consequences of aphasia for the stroke survivor and carer.

Current research interest:
Health services research arising from the National Stroke Unit Program aiming to increase access to coordinated stroke services throughout Australia. Translation of research into practice at all levels of intervention – awareness of stroke, stroke risk factors, hyperacute interventions, allied health interventions, psychosocial aspects and long term recovery. Evaluation of outcomes after speech pathology intervention in the acute phase. Psychosocial consequences of stroke and appropriate interventions for chronic needs. Currently co-supervising two PhD students looking at acute aphasia interventions and factors in positive recovery for verbal dyspraxia.

Relevant Publications

NAME: DR CHRISTOPHER LEVI

Position and Institution: Staff Specialist/ Conjoint Senior Lecturer in Neurology

Contact Details: Department of Neurology, John Hunter Hospital
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Email Christopher.Levi@hunter.health.nsw.gov.au

Qualifications: B. Med. Sci University of New South Wales
M.B.B.S.University of New South Wales (Honours Class II Div I)
F.R.A.C.P. R.A.C.P

Research Experience:
3. Hunter Medical Research Project Grant (Dr Andrew Lojszczyk Memorial Award) – 1999. 10% dextran 40 in the prevention of stroke complicating carotid endarterectomy.
5. Australian Brain Foundation (NSW Branch) Research Grant. Brain impairment after cardiac surgery.

Current Research Interest:
Major interests are in clinical applications of neurovascular ultrasound, acute stroke therapies, antithrombotic therapies, stroke prevention, and health systems change in stroke care. Dr Levi chairs the Management Committee of the multicentre randomised controlled trial of dextran in the prevention of stroke complicating carotid surgery (DICE trial) and sits on the Steering Committee of the Aortic Arch Related Cerebral Hazard (ARCH) study and the
Stroke Thrombolysis: extending the time window with MRI study. He is founding co-chairman of the Australasian Stroke Unit Network, Lead Clinician in the Royal Australasian College of Physicians sponsored Clinical Support Systems Project “Towards a safer Culture” and Chairman of the NSW Greater Metropolitan Transition Taskforce Stroke Co-ordinating Committee.

Relevant Publications:

NAME: DR GABRIEL LIBERATURE

**Position and institution:** Research Fellow (NH&MRC), Department of Medicine University of Melbourne, Austin Hospital

**Contact details:** 9496-3257 (work), 0414 463956 (mobile), g.liberatore@unimelb.edu.au (email)

**Qualifications:** BSc (Hons), Ph.D., MBA.

**Research experience:** Upon completion of a Bachelor of Science (Biochemistry) degree with honours year at the University of Melbourne, Dr Liberatore 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 his Ph.D. in early 1998, he was employed as a Post-Doctoral Research Fellow in the Department of Neurology, Columbia University, New York focusing on the mechanisms that underlie neurodegeneration in Parkinson’s disease. Upon return to Australia he 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. In September 2001 he returned to the Dept of Medicine/Neurology (A&RMC) and has continued to work on neuroregeneration/neuroprotection aspects of ischaemic stroke in animal models.

**Current research interest:** Current research interests lie in understanding the mechanisms that lead to tPA neurotoxicity in addition to the evaluation of novel neuroprotectants and thrombolytics (Desmotaplase) in animals models of ischaemic stroke.

**Relevant publications:**


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**NAME:** MR INDRA LIM

**Position and Institution:** Computer Programmer

**Contact details:** (03) 9496 3114

**Qualifications:** Bachelor of Applied Science (Hons)

**Research Experience:** Machine Vision – facial recognition

**Current research interest:** Kinetic model for the brain

---

**NAME:** DR POH-SIEN LOH
NAME:   DR HENRY MA

Position and Institution: Neurology registrar Royal Melbourne Hospital

Contact Details : (w) 93427000, (H) 98421924, (Mobile) 0402309822

Qualification : MBBS, FRACP Advanced Trainee

Research Experience : Clinical recruitment of stroke trials

Current Research interest : Stroke imaging in penumbra

Publications :  


Ma H, Images in neuroscience, A case of Erheim - Chester disease; (submitted 2003)


NAME:   DR MALCOLM MACLEOD

Position and Institution: Clinical Research Fellow, NSRI & Honorary Fellow, University of Edinburgh

Contact details: Malcolm@apoptosis.freeserve.co.uk

Qualifications: BSc MBChB MRCP PhD

Research Experience: 5 years post - doc

Current research interest: Why neuroprotectants don’t work

Relevant publications (no more than 10):  


Curricula Vitae


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<th>NAME: DR ROMESH MARKUS</th>
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**Position and Institution:**
- Staff Specialist, Neurology
- Director, Stroke Unit
- St Vincent’s Hospital
- Victoria Street, Darlinghurst, NSW 2010

**Contact details**
- rmarkus@stvincents.com.au
- 61 2 8382 4103 (Tel)
- 61 3 8382 3237 (Fax)

**Qualifications**
- MBChB(Hons) FRACP

**Research Experience:** Research Fellow, NSRI

**Current research interest:** Imaging the ischemic penumbra

**Relevant publications (no more than 10)**

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<th>NAME: MS MARJ MOODIE</th>
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**Position and institution:** Research Fellow, Program Evaluation Unit, School of Population Health, The University of Melbourne

**Contact details:** Tel: 03 8344 0662; Fax: 03 9348 1174; marjory@pgrad.unimelb.edu.au
Qualifications: BA (Hons); Dip. Educ.; Dip. TRP; Dpub Health (pending)

Research experience: Program evaluation and health services planning. Economic evaluation of different models for stroke service delivery and interventions for stroke.

Current research interest: The use of the MORUCOS (A Model of Resource Utilisation, Costs and Outcomes of Stroke) to assist priority setting in stroke.

Relevant publications:


NAME: MR IAN T MOSLEY

Position: Research: Fellow and PhD Student

Contact details: Phone: 94962842
e-mail: ian.mosley@austin.unimelb.edu.au

Qualifications: M.Bus (Management) B.Bus.(Accounting) G.Dip. (Health Admin.) G.Dip. (Education) R.N. (RMH)

Research Experience: PhD Student, Research Supervisor M.Bus Students RMIT Business

Research Interest: Pre-hospital and Emergency Management of Stroke Patients

NAME: MRS SUE MOSLEY

Position: Research: Nurse NEMESIS

Contact details: Phone: 94962557
e-mail: s.mosley@austin.unimelb.edu.au

Qualifications: Registered Nurse

Research Experience: Data collection and patient interviews NEMESIS

Research Interest: Community Education and Stroke Prevention
NAME: DR RACHEL MULLIGAN

Position and Institution: Radiochemist, University of Melbourne PET Centre, Austin Campus, Austin Health Level 1 Harold Stokes Building Studley Rd, Heidelberg, VIC 3084

Contact details: Phone: 94965669 Email rmulligan@austin.unimelb.edu.au

Qualifications:
• Doctor of Philosophy in Nuclear Medicine, University College of London, UK.
• Masters of Science in Cell Biology, University of Canterbury, New Zealand.
• Bachelor of Science in Zoology, University of Canterbury, New Zealand.

Research Experience:
Institute of Nuclear Medicine, University College of London, London, UK.
Research Radiochemist: My research involved the investigation of diverse aspects of radioligand development that could potential influence quantification of receptor binding including $^{123}$I-labelling reaction conditions, radioligand stability in vitro and in vivo metabolism. I was employed on two sequential Medical Research Council grants examining the role of various brain receptors in schizophrenia with SPET and PET.

ENDOLAB, Christchurch Public Hospital, Christchurch, New Zealand
Technician on a Medical Research Council grant investigating putative and occult factors controlling the release of ACTH from equine anterior pituitary cells in vitro.

Current research interest: I am interested in the development and validation of PET radioligands for imaging epilepsy and stroke.

Publications
NAME: **MS TORI O’COLLINS**

**Position and Institution:** PhD Student, NSRI / University of Melbourne

**Contact details:** Tel: +61 3 9496 3257    Email: toriocollins@ziplip.com

**Qualifications:** B.Sci

**Research Experience:** Current research in David Howell’s Neuroscience Lab, ARMC.

**Current research interest:** Neuroscience

**Relevant publications (no more than 10):**

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NAME: **DR MARK PARSONS**

**Contact details:**
Department of Neurology
John Hunter Hospital
Lookout Road New Lambton NSW
Australia

**Qualifications:**
B Med (University of Newcastle) 1991
FRACP 1998
Ph D (University of Melbourne) 2003

**Current Appointments**

- **Staff Specialist in Neurology,** John Hunter Hospital, Newcastle.
- **Director of Stroke Unit,** Mater Misericordiae Hospital, Newcastle.
- **Honorary Neurologist,** Department of Neurology and University of Melbourne
  Department of Medicine, Royal Melbourne Hospital.
- **Conjoint Senior Lecturer,** Faculty of Medicine, University of Newcastle.

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NAME: **MS SAUNA PAUL**

**Position and Institution:**
PhD Research Fellow,
National Stroke Research Institute, Epidemiology Division

**Contact details:**
Ph: 03 9496 2782
e-mail: spaul@austin.unimelb.edu.au

**Qualifications:** BSc (Hons) Physiology
Curricula Vitae

Research Experience:

Honours year undertaken at The Ritchie Centre for Baby Health Research. The study involved examining the control of cerebral blood flow in chronically instrumented newborn lambs.

Current research interest:

Stroke epidemiology. In particular, the long-term outcome of stroke survivors and how the management of stroke risk factors may affect long-term outcome (in terms of mortality, recurrence, functional outcome and quality of life).

Relevant publications (no more than 10):


<table>
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<tr>
<th>NAME:</th>
<th>MS DORA PEARCE</th>
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Position and Institution: Biostatistician, NSRI

Contact details: Phone 9496 2067; email dpearce@austin.unimelb.edu.au

Qualifications: Bachelor of Applied Biology, Graduate Diploma in Epidemiology, *Master of Information Technology by Research*

Research Experience: I have undertaken statistical analyses relating stroke outcomes to acute and community-based care interventions, adjusted for case-mix; provided statistical support for an economic evaluation to ascertain cost-effectiveness of stroke treatment options; and provided statistical support for varied stroke-related research projects. Previously, I worked as a hospital scientist until moving into the area of public health research in the Department of Community Medicine, University of Melbourne, located at the Ballarat Base Hospital.

Special research interest: The application of spatial statistical techniques, incorporating the use of a geographic information system, to investigate variation in health outcomes by geographic location.

Curricula Vitae


NAME: DR BRUNO PEDREIRA

Institution: Stroke Research Fellow
National Stroke Research Institute
Austin & Repatriation Medical Centre

Qualifications

1999 – 2001 Clinical Neurology Resident
Hospital São Rafael, Salvador, BA, Brazil

2002 – 2003 Stroke Registrar
Austin & Repatriation Medical Centre

Current Research interest
Stroke - Neuroimaging

Abstracts
Pedreira B, Azevedo A. Action, mechanisms and effects of cocaine 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

2º Brazilian Meeting on Cerebrovascular Diseases, Rio Quente, GO. 1999

XIX Brazilian Meeting of Neurology, Salvador, BA. 2000


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**NAME: DR THANH G PHAN**

Position and Institution: Fellow

Contact details: 94963114

Qualifications: FRACP

Research Experience: MRI

Current research interest: Applications of MR imaging in acute stroke

Relevant publications (no more than 10)


NAME: DR JANE PROSSER

Position and Institution  Research Fellow, Royal Melbourne Hospital

Contact details  jane.prosser@mh.org.au

Qualifications  MBBS FRACP

Research Experience

Current research interest  Imaging in acute stroke and stroke recovery

Relevant publications (no more than 10)

NAME: PROFESSOR DAVID CHARLES REUTENS

Professor of Neurosciences, Monash University and Director of Neurology, Monash Medical Centre

Academic Qualifications

M.B.  B.S.  University of Western Australia, 1984.
M.D.  University of Melbourne, 1993.

Past Appointments

1985-1989  Intern, Resident Medical Officer, Neurology Registrar, Royal Perth Hospital.
1990  Ciba-Geigy Fellow in Epileptology, Austin Hospital.
1991-1992  NH&MRC Medical Postgraduate Scholar
July 1993-1995  NH&MRC Neil Hamilton Fairley Travelling Fellow
1996-1998  Assistant Professor, Department of Neurology & Neurosurgery, McGill University.
           Staff Neurologist, Montreal Neurological Hospital, Montreal, Canada.
1998-1999  Staff Neurologist, Royal Victoria Hospital, Montreal, Canada.
           Senior Research Fellow (NH&MRC Clinical Centres of Excellence Grant)
1999-2003  Principal Fellow with the title of Associate Professor, Department of Medicine, The University of Melbourne, Austin & Repatriation Medical Centre, Heidelberg, Victoria.
Curricula Vitae

Neurologist, Austin & Repatriation Medical Centre, Heidelberg, Victoria.
Head, Neuroimaging Division, National Stroke Research Institute, Austin & Repatriation Medical Centre, Heidelberg, Victoria.
Head, PET Neuroscience Research, Centre for PET, Austin & Repatriation Medical Centre, Heidelberg, Victoria.

NAME: MS ANTONELLA SCARDAMAGLIA

Position and Institution Clinical Trials Co-ordinator NSRI

Contact details #2648

Qualifications Bachelor of Health Sciences Nursing
Research Methods 3

Research Experience Current appointment

Current research interest Acute stroke trials, plus secondary prevention study, ARCH

Relevant publications (no more than 10)

NAME: DR KARIN SITTE

Position and institution: Manager, Austin Node, Neurosciences Victoria. Manager Neuroimaging Platform (National Neuroscience Facility)

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, Grad Cert Man (Technology Management)

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: DR NEIL SPRATT

Position and Institution: PhD Student/Neurology Trainee, University of Melbourne/ NSRI basic science laboratory/ Austin Health

Contact details: Medicine/Neurology
Level 7, Lance Townsend Building
Austin Health, Studley Rd
Heidelberg 3084
Email: n.spratt@pgrad.unimelb.edu.au


Clinical – Co-investigator in several stroke research trials including: ASTIN, EPITHET, DICE, MATCH.

Current research interest: The use of FMISO to image the ischaemic penumbra in animal stroke models.

Relevant publications (no more than 10):


NAME: DR VELANDAI SRIKANTH

Position and Institution: Post-Doctoral Fellow, Menzies Research Institute, Hobart, Tasmania.
Contact details: email: velandai.srikanth@utas.edu.au

Qualifications: PhD

Experience: PhD in cognitive epidemiology related to stroke in NEMESIS

Current research interest: Mainly in pursuing further areas of research in above area; also involved in population-based musculoskeletal epidemiology.

Relevant publications (no more than 10)

NAME: DR JONATHAN STURM

Position and Institution
Staff Specialist Neurologist, Central Coast Area Health, Gosford, NSW.
Senior Research Fellow, National Stroke Research Institute.

Contact details
Dept of Neurology, Gosford Hospital.
PO Box 361, Gosford, NSW 2250.
Phone: 02 4320 3932
Fax: 02 4320 3783
Email: jwsturm@doh.health.nsw.gov.au

Qualifications
MBChB, PhD, FRACP.

Research Experience
Current research interest
2003 – ongoing. Currently developing studies in the areas of post-stroke depression; genetic risk factors for stroke; and post-stroke nutrition.

Relevant publications

NAME: DR MANDY THRIFT

Position: NH&MRC Research Fellow

Institution: Epidemiology Division, National Stroke Research Institute

Contact details: National Stroke Research Institute, Level 1, Neurosciences Building, Austin Health – Repatriation Campus, 300 Waterdale Road, Heidelberg Heights 3081, Australia. Phone (613) 9496-2862, Fax: (613) 9496-2650, email thrift@unimelb.edu.au

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

Research experience: 13 years working in stroke epidemiology to identify risk factors for primary intracerebral haemorrhage, to determine incidence of stroke in a region of Melbourne, and to assess short and long term outcome of stroke (survival, stroke recurrence, disability, handicap, quality of life), management of risk factors, and costs of stroke.

Current research interest: Stroke prevention, ethnic difference in stroke incidence, and long term outcome of stroke.

Relevant publications


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**NAME:** MS LENA VAN RAAY

Position and Institution: Technical Assistant, Department of Medicine, University of Melbourne, Austin & Repatriation Medical Centre and National Stroke Research Institute

Contact details: ph (03) 94965635 email lvr@unimelb.edu.au

Qualifications: Bachelor of Applied Science (Animal Science)

Research Experience: (Feb 2002) Research Assistant/Animal Technician at the Howard Florey Institute of Experimental Physiology and Medicine, Neurobiology and Homeostasis Unit. The University of Melbourne. Work involved investigation of angiotensin and thermoregulation with rats and sheep.

Current research interest: (2003-ongoing) Working as part of the Stroke Research Team in David Howells laboratory. Investigating the neuroprotective effects of novel compounds on transient ischemic injury in a rat model of stroke.

Relevant publications (no more than 10)
NAME: DR PATRICK C A J VROOMEN

Position and Institution: Stroke Registrar, Austin & Repatriation Medical Centre

Contact Details: pcajvr@yahoo.com, 23 Lochabar Court 3079 Ivanhoe

Qualifications: Registered Neurologist Royal Dutch College of Medicine, M.D., Ph.D.

Current research interest: Neuronal plasticity

Relevant publications:
2. Vroomen PCAJ, de Krom MCTFM, Knottnerus JA: Diagnostic value of history and physical examination in patients with sciatica due to disc herniation; a systematic review. J Neurolog: 246(1); 899-906, 1999.

NAME: DR JOHN WILLIAMS

Position and Institution: MR Physiologist, NSRI, and Howard Florey Institute.

Contact details: c/- Howard Florey Institute
The University of Melbourne
Melbourne, VIC, 3010
Tel: 03-8344-6606 Fax: 03-9348-1707
Email: j.williams@hfi.unimelb.edu.au

Qualifications: BSc (Hons I), PhD (in preparation).

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; 6 years experience with Bruker systems (Biospec 47/30 DBX, AMX300 &400); 14 years experience preparing and running in vivo and ex 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 interest:

Imaging of stroke and infarct salvage with potentially neuroprotective compounds in the dwarf pig (and rat) using MRI and histological techniques, combined with neurobehavioural testing.

Relevant publications (no more than 10):


NAME: DR PETER WRIGHT

Position and Institution: Consultant Neurologist, Waikato Health, Hamilton, New Zealand. Fellow NSRI.

Contact details: Hm: ph *64 7 827 3980 Wk pager *64 7 839 8899 Mb *64 21 766 363

Qualifications: MBChB, FRACP

Research Experience: 3.5 yrs towards a PhD, as a fellow at the NSRI.

Current research interest Using Magnetic Resonance Imaging Of The Ischaemic Penumbra to Determine The Impact Of Physiological Variables On Stroke Outcome In Humans.

Relevant publications

Curricula Vitae


- Diffusion and Perfusion Weighted MRI predicts response to thrombolysis in stroke. Mark W. Parsons, FRACP; P.Alan Barber, PhD, FRACP; Jonathon Chalk, PhD, FRACP; David G. Darby, PhD, FRACP; Stephen Rose, PhD; Patricia M. Desmond, MD. FRACR; Richard P. Gerraty, MD, FRACP; Brian M. Tress, MD, FRACR; Peter Wright, FRACP; Geoffrey A. Donnan, MD, FRACP; and Stephen M. Davis, MD, FRACR. Annals of Neurology. 2002 Jan;51(1):28-37.


- MRI in Stroke: Chapter: The Ischaemic Penumbra. CUP. Geoffrey A Donnan, Peter M Wright, Romesh Markus, Thanh G Phan, David C Reutens

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NAME: MR DENNIS YOUNG

Position and Institution
Clinical Trials Manager
National Stroke Research Institute

Contact details
Level 1, Neurosciences Building
Austin Health
300 Waterdale Road
Heidelberg Heights, Victoria 3081
Australia
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 – 2001
Clinical Trials Manager, NSRI 2001 - present

Current research interest
National Coordinator for:
Dextran in Carotid Endarterectomy (DICE) Study
Aortic arch Reduced Cerebral Hazard (ARCH) Study

Relevant publications (no more than 10)
Nil
Awards

Retreat Awards

The Bravery Award: Presented to Amanda Gilligan for having the steely resolve to sign up for horse-riding given the tragic circumstances that occurred last year.

The Mr Nice Guy Award: Presented to Bevyn Jarrott for feeding his rats Irish coffee.

The Laboratory Leadership Award: Presented to David Howells for encouraging his laboratory staff to join him on his rugby sabbatical.

The Annual Most Considerate Partner Award: Presented to Dugald McAdam for sacrificing his spinal hygiene to child entertainment.

The Rat Friendly Society Award: Presented to Gab Liberatore for showing such keen interest in the treatment of stroke in rodents (PS for God’s sake don’t tell the emergency room physicians).

The Winelovers (it’s good for you) Award: Presented to Geoffrey Donnan for disguising his search for red wine as the behaviour of a gracious host.

The Most Devoted (and Wisest) Board Member Award: Presented to Graeme Bowker for attending the Retreat.

The Most Humiliated Spouse Award: Presented to Mandy Thrift for putting up with her husband’s embarrassing retreat behaviour year after year!

The Master of Technology Award: Presented to Neil Spratt for mistaking the Off button for the Laser button.

The Golfer Least Likely to Succeed Award: Presented to Patrick Vroomen for failing to understand the out of bounds rule.
The Best Legs Award: Presented to Stephen Davis for the ability to wear lycra shorts in the foyer without scaring small children

The Most Resilient Delegate Award: Presented to Thanh Phan for overcoming sleep deprivation and remaining conscious through at least part of this morning’s session considering his burden of work and childcare responsibility

The Four Slide Award: Presented to Tori O’Collins for the most creative slide counting