

*Institute of
Clinical
Neurosciences*

Frenchay Hospital,

BRISTOL

BIRU

BNI

Bristol Alzheimer's Research Group

Laryngeal Research Group

Neonatal Neurology

Neuroepidemiology

Neurogenetics

Neurology

Neuropathology

Neurophysiology

Neuropsychiatry

Neuropsychology

Neuroradiology

Neurosurgery

Paediatric Neurology

SLTRU



UNIVERSITY
OF BRISTOL



BURDEN
NEUROLOGICAL
INSTITUTE

North Bristol 
NHS Trust

*The Institute
of Clinical
Neurosciences*

*Second Annual Report
2002*

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Introduction

The second year of the **Institute of Clinical Neurosciences** has been one of very successful development and growth. Building upon the base described in last year's Report, significant new developments have been implemented in the pursuit of excellence in research and teaching in the clinical neurosciences. A number of new neuroscience groups have joined the ICN, new projects have commenced, new positions created, new buildings planned and new teaching activities executed. An extremely high profile in both the scientific world and in the lay media was achieved by the highly promising preliminary results of the pioneering neurosurgical pilot trial treating Parkinson's disease patients with growth factor infusions. The breadth, depth and indeed success of our research activities is again objectively demonstrated in the 97 publications in 2002, and the total of over £7.5m. grant and other research-related income.

As described last year, we confidently aspire towards a new-build, bricks-and-mortar *Neurosciences Institute*, accommodating first-class clinical neuroscience research, teaching and the whole spectrum of integrated clinical neuroscience patient care. Whilst future potential opportunities for funding such an ambitious development may have begun to emerge on the horizon, for the time being the ICN remains a confederation rather than a building. We have not, however, lost sight of this goal, and the University of Bristol in its recent External Review of academic medicine explicitly encouraged the development of such a project.

The core ICN groups at the beginning of the 2001-2002 period included the Burden Neurological Institute, the Bristol Alzheimer's

Research Group, the Brain Injury and Rehabilitation Unit, the Speech and Language Therapy Research Unit, and the departments of Neurology, Neuropathology, Paediatric Neurology, Clinical Neurogenetics, Neurosurgery, Neuroradiology, Neurophysiology, Neuropsychology, and Neuropsychiatry. In late 2001, the Neonatal Neurology Group led by Professor Andrew Whitelaw and Dr Marianne Thoreson, with the integral involvement also of Professor Ian Silver, joined the ICN, bringing their high-profile research interests in neonatal acute brain injury. The rapidly growing Academic ENT Laryngeal Research Group also joined at this time; led by Professor Martin Birchall, the group is particularly interested in the immunology and innervation of laryngeal transplants. In mid-2002, Dr Yoav Ben-Shlomo, a Neuroepidemiologist in the University of Bristol Department of Social Medicine, also joined the Academic Committee, bringing a further area of internationally-recognised expertise to the ICN.

The fundamental aims and aspirations of the Institute of Clinical Neurosciences have not changed and are worth rehearsing : -

- to achieve and maintain excellence in clinical neuroscience research and teaching;
- to provide a vehicle for regular scientific communication, cooperation and collaboration between clinical neuroscience-related research groups within North Bristol;
- to encourage and facilitate neuroscience research and teaching activity in clinical units currently dedicated primarily to the delivery of patient care;
- to stimulate and facilitate the *de novo* development of new clinical neuroscience research groups in North Bristol;
- to improve communication and collaboration between North Bristol neuroscience research and basic and related neuroscience groups within the University of Bristol, UBHT and UWE;
- to improve and co-ordinate aspects of clinical neuroscience undergraduate and postgraduate education and training;
- to work towards the development of a proposed major new-build ***Institute of Clinical Neurosciences***.

Whilst these aims remain constant, our continued and successful growth and expansion, and the achievement of critical scientific mass, have emphasised the importance of an established, clear and identifiable research strategy - to inform future planning, to act as catalyst for future developments, to help the ICN develop its own identifiable and recognisable character and research footprint, and publicly

to demonstrate a coherent and themed collective approach focussing in particular on certain clinically relevant areas of neuroscience endeavour. The ICN does not conveniently fit into any of the current University Departmental administrative structures, accommodating as it does groups whose University affiliations include Hospital Medicine, Child Health, Pathology and Microbiology, Surgery, and Psychology. We see this as a distinct strength – the potential for multi-disciplinary collaboration is a major component of our aims and objectives, and has already yielded new interdepartmental projects and liaisons. We are, however, alert to the possible perceived danger of lack of cohesion: another reason for developing a strategic approach to our subject is to illustrate and emphasise the principle of association by research theme, rather than University Department, and bridging both administrative and geographical boundaries.

Despite the number and – at first glance – the diversity of the many successful research groups in the ICN, our principal research activities in the fields of neonatal neurology, otoneurology, multiple sclerosis and dementia, and in other areas too, are inherently underpinned by two clear neurological themes: Preventing Damage, and Promoting Regeneration, with clinical and experimental neuropathology representing a vital core running through all these activities. Translational neuroscience - projects and programmes which start with conventional laboratory-based cellular and molecular biology, but which are designed to bridge the gap between laboratory and the clinical application of experimental studies - has always represented the underlying motif of the ICN, and continues to bind together the broader but more thematic research of the larger grouping. The current and expanding complement of basic and clinical neuroscientists in a number of inter-related and interdependent disciplines, including senior clinicians within the ICN with extensive experience in running clinical trials, is well-placed to implement the timely progression from bench science to clinical studies yielding real benefits for patients.

Neil Scolding FRCP, PhD

Burden Professor of Clinical Neurosciences

Director, Institute of Clinical Neurosciences

The Institute of Clinical Neurosciences

Structures and Committees

Board of Governors

Chairman

Professor Ian Silver

Professor Stephen Lisney,

Dean, Faculty of Medicine & Dentistry

Professor David Nutt,

Dean of Clinical Medicine

Representing the University of Bristol

Mr Tony Woolgar,

Chief Executive

Professor Seth Love,

Clinical Director, Neurosciences

Representing the North Bristol NHS Trust

Mr Tony Checkley,

Chairman, Council of the Burden Neurological Institute

Dr Pauline Begley,

Vice-Chairman, Council of the Burden Neurological Institute

Representing the Burden Neurological Institute

The Institute of Clinical Neurosciences

Academic Committee

<i>Chairman:</i>	<i>Neil Scolding,</i> <i>Burden Professor of Clinical Neurosciences,</i> <i>Director, Institute of Clinical Neurosciences</i>
<i>Academic ENT</i>	<i>Prof Martin Birchall</i>
<i>Academic Neurology</i>	<i>Dr Ian Ormerod, Head of Specialty</i>
<i>BIRU</i>	<i>Dr John Holloway, Director</i>
<i>BNI</i>	<i>Dr Stuart Butler, Director</i>
<i>Clinical Neurosciences Education</i>	<i>Dr Marguerite Hill</i>
<i>Dementia Research Group</i>	<i>Professor Gordon Wilcock, Director</i>
<i>Neonatal Neurology</i>	<i>Prof Andrew Whitelaw</i>
<i>Neuroepidemiology</i>	<i>Dr Yoav Ben-Shlomo</i>
<i>Neurogenetics</i>	<i>Dr Linda Tyfield, Head of Dept.</i>
<i>Neuropathology</i>	<i>Prof Seth Love, Head, Academic Dept.</i>
<i>Neurophysiology</i>	<i>Dr Nick Kane, Head of Specialty</i>
<i>Neuropsychiatry</i>	<i>Dr Jonathan Bird, Head of Specialty</i>
<i>Neuropsychology</i>	<i>Ms Renee McCarter, Head of Specialty</i>
<i>Neuroradiology</i>	<i>Dr Shelley Renowden, Academic Lead</i>
<i>Neurosurgery</i>	<i>Mr Rick Nelson, Head of Specialty</i>
<i>Paediatric Neurology</i>	<i>Dr Peta Sharples, Head of Specialty</i>
<i>SLTRU</i>	<i>Dr Sue Roulstone, Director</i>
<i>Representing</i>	
<i>University Basic Neurosciences</i>	<i>Dr Richard Greene, Dept. Anatomy</i>

Grant Support

Action Research	The role of computers for independent practice by patients with dysarthria	Dr S Roulstone	£116,000
Action Research	The pathological role of transforming growth factor (TGF) β and possible therapeutic role of anti-TGF β in a piglet model of post-haemorrhagic ventricular dilatation	A Whitelaw, M Thoresen, H Porter, S Love	£115,470
Action Research	Relationship between impaired gait and eye movements in cerebellar ataxia, Parkinson's disease and cerebral palsy.	Dr IT Ferguson	£78,501
Alzheimer's Research Trust	Molecular Screening for Mimetics of NGF: a therapeutic option in Alzheimer's disease	Dawbarn, D Allen SJ Sessions RB Wilcock GK	£456,355
Alzheimer's Research Trust	The establishment of an Alzheimer's Research Trust Network	Prof. G Wilcock	£109,500
Alzheimer's Society	The pattern and causes of asymptomatic cognitive decline leading to dementia	Dr Y Ben Shlomo Dr Gallagher J Dr Ebrahim S	£154,065
Biotechnology and Biological Sciences Research Council	Early pathogenesis in prion disease.	Dr S Betmouni R Greene	£149,000
BRACE	The clinical and pathological role of cerebral amyloid angiopathy in Alzheimer's disease	Professor S Love GK Wilcock	£35,000
BRACE	An evaluation of different genetic polymorphisms as contributory factors for AD	Professor GK Wilcock	£50,000
BRACE	The extracellular matrix in Alzheimer's disease	Professor S Love GK Wilcock	£54,000
BRACE	Infrastructure for clinical and clinical genetic research into Alzheimer's and other dementias	Professor GK Wilcock	£115,000
The Burden Trust	Core grant	BNI	£45,000
Champions of Child Health.	Drainage, Irrigation and Fibrinolytic Therapy (DRIFT) for posthaemorrhagic hydrocephalus.	Prof A Whitelaw	£13,000.
Charitable	A pilot study of the safety and effectiveness of the Traxon Spinal Cord Repair Stimulator for the treatment of complete spinal cord injury.	Mr C Bolger	£6,000
Charitable/Donations	Choroid plexus coagulation for post-haemorrhagic hydrocephalus	Mr I Pople	£2,000
Charitable/Donations	A regional study of cerebral vasculitis	Prof N Scolding	£100,000
CLIC	The effect of brain tumours on the child and family	Dr P Sharples	£110,000
Codman, Johnson & Johnson Professional Inc (Donation)	A prospective, randomised, controlled trial to evaluate the efficacy & safety of endoscopic choroid plexus coagulation with third ventriculostomy in the treatment of idiopathic normal pressure hydrocephalus (ISRCTN29863839)	Mr I.K. Pople Mr R.J. Edwards	£28,000
Commercial/Industrial	A randomised, double-blind study to compare the efficacy and safety of Neurobloc (Botulinum toxin Type B) with Botulinum toxin Type A (Botox) in patients with Cervical Dystonia who have never previously received a Btoxin	Dr P Heywood	£14,650

Community Fund	Improving the diagnosis and treatment of attention deficits in head injured patients.	Dr D. Polo	£149,000
Cranfield Impact Centre, Cranfield University	Predictive models of fatal head trauma	Dr T Moss	£2,400
D.E.F.R.A	Development of novel method for stunning food animals	Prof S. Love Dr H. Anil Dr S Butler	£250,000
Department of Health	Neuropathological spectrum of human transmissible spongiform encephalopathies: Relationship with atypical dementias: a national retrospective review (Bristol element)	Dr T H Moss	£94,508
Endowment	A multicentre double-blind study of the efficacy and safety of alternative therapies in patients with newly diagnosed epilepsy	Dr J M Bird	£50,900
Endowment	Evaluation of the long term clinical effectiveness of a drug therapy in epilepsy; an open label, follow up study of patients established on monotherapy with alternative therapies.	Dr J M Bird	£12,000
Endowment	GDNF infusion into the putamen for the treatment of advanced Parkinson's Disease.	Mr S Gill	£500,000
Endowment	Oral glatirimer acetate in relapsing remitting multiple sclerosis.	Professor N J Scolding	£41,400
Endowment	Randomised, double-blind, placebo controlled study of add-on additional therapy in subjects with seizures (any type) and learning difficulties (mental handicap)	Dr J M Bird	£12,000
Food Standards Agency, MO3012	Prevalence of CNS embolism and the determination of its potential for visceral dissemination at stunning and slaughter in cattle	MH Anil DA Harbour S Love	£370,000
Food Standards Agency, MO3013	Prevalence of CNS embolism and the determination of its potential for visceral dissemination at stunning and slaughter in cattle	MH Anil DA Harbour S Love	£153,000
Health & Safety Executive	Molecular mechanisms of glutathione-depleting neurotoxins	Dr T Benn	£8,827
Hospital Savings Association Charitable Trust	A study to investigate health beliefs of people with non-epileptic seizures (NES) and people with chronic fatigue syndrome (CFS)	Mr A Green	£5,000
Jules Thorn Charitable Trust	Studies to characterise the T cell response to a possible immunodominant epitope in the epsilon subunit of the acetylcholine receptor in Myasthenia Gravis	Dr M E Hill	£10,000
Medical Research Council	Oxidative stress in prion disease – an electrophysiological and neuropathological study	R Greene, S Betmouni S Love	£33 000
Medical Research Council	Whole body Hypothermia for the Treatment of Perinatal Asphyxial Encephalopathy.	Dr M Thoresen Prof A Whitelaw	£ 130,000.
Medical Research Council	Premorbid influence of apolipoprotein E genotype on synaptic density in the adult human brain	S Love, S Allen, S MacGowan, GK Wilcock,	£218,260

Multiple Sclerosis Society of GB and NI	The cell culture and study of adult human oligodendrocytes.	Professor N J Scolding	£124,610
Mobile Telecommunications And Health Research Programme (DoH)	Detection of the effects of microwave radiation on the electrical activity of the brain	Dr S.R.Butler	£100,045
National R & D Commissioned Research	Disability due to head injury in childhood	Dr P Sharples	£370,470
NHS Executive (Health Technology Assessment Programme)	Controlled trial of microdiscectomy for lumbar disc herniation	Mr R J Nelson	£132,149
NHS Executive (S & W Regional R&D Directorate)	Speech and Language Therapy Evaluation Programme	Dr S Roulstone	£286,709
NHS Executive (S & W Regional R&D Directorate)	A prospective follow-up of a cohort of children referred to speech and language therapy for early speech/language delay.	Dr S Roulstone	£110,117
Olympic Medical (Seattle)	Brain - Cooling for the Treatment of Perinatal Hypoxic-ischaemic encephalopathy	Prof A Whitelaw Dr M Thoresen	£20,000
Parkinson's Disease Society	Repetitive transcranial magnetic stimulation for levodopa	Dr S. Filipovic Dr P Heywood	£95,000
Parkinson's Disease Society	A large randomised long-term assessment of the relative effectiveness of surgery for Parkinson's disease.	Mr S S Gill	£250,000
Parkinson's Disease Society	GDNF infusion into the putamen for the treatment of advance Parkinson's Disease.	Mr S S Gill	£94,000
Patrick Berthoud Charitable Trust	The role of the human oligodendrocyte progenitor in remyelination in multiple sclerosis	Prof N Scolding Dr H Wilson	£100 000
PPP Healthcare Medical Trust	Randomised trial of an intervention to reduce maternal stress and infant developmental delay after very premature birth.	Prof A Whitelaw	£502,000
PPP Healthcare Medical Trust	An evaluation of a psycho-educational intervention in older adults with mild cognitive impairment using a randomised controlled trial and n=1 methodology	Bucks RS, Emmerson C, Spaull D, Wilcock GK	£48 000
RNHRD, Bath Donated Funds	Sensorimotor integration in complex region pain syndrome	Dr A.J.Turton Dr S. Filipovic	£3580
Royal Society	Inflammation in Neurodegeneration.	Dr S Betmouni	£9,971
Southmead Research Foundation	Genetic basis of brain injury in preterm babies.	Prof A Whitelaw Dr S Renowden Dr A Millar.	£ 30,000.
SPARKS	Is hypothermia after brain injury only neuroprotective if you are anaesthetized?	Dr M Thoresen.	£ 23,600.
Teva Pharmaceuticals & Serono	Multiple Sclerosis Clinical Research Fellowship	NJ Scolding	£76 200
Stroke Association	Does use of a daily muscle stretch regime prevent development contractures and muscle stiffness in stroke patients?	Dr A J Turton	£117,680
The Stroke Association	Development and evaluation of remote speech and language therapy for dysphasic individuals	Dr S Roulstone	£86,000
The Underwood Trust	Investigating the efficacy of computer assisted therapy	Dr S Roulstone	£544,442
The Underwood Trust	A study of the effectiveness of the Lidcombe approach to therapy for children who stammer	Dr S Roulstone	£184000
The Underwood Trust	The development of regional networks for the provision of speech and language therapy for people who stammer	Dr S Roulstone	£19500

The Underwood Trust	Computerised therapy for children	Dr S Roulstone	£40000
The Underwood Trust	Use of a voice recognition software by people with aphasia: an investigation	Ms J Wade	£25,000
University of Bristol	Oligodendrocyte progenitors in health and in the lesions of multiple sclerosis	Prof. N Scolding	£60,000
Unknown	A randomised controlled trial of microdiscectomy and conservative disc surgery for sciatica and discogenic back pain	Mr R J Nelson	£104,573
Wellcome Trust	Keeping a cool head	Dr M Thoresen Prof. N I. Silver	£ 452,000
Wellcome Trust	The mechanisms of recovery and persistent disability following relapses in multiple sclerosis and optic neuritis	Prof. N Scolding	£164,237
Wellcome Trust	The cell culture and study of adult human Schwann cells.	Prof. N Scolding	£166,237

Total current support: £ 7, 614 286

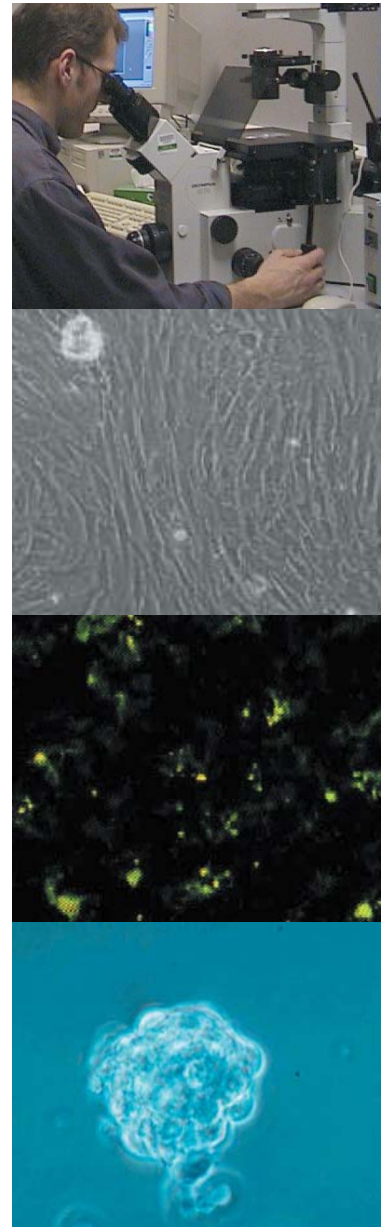
Academic Neurology

The Multiple Sclerosis Group

The *Multiple Sclerosis Research Group's* activities continue to centre in particular on the underlying cell biology of multiple sclerosis and the development and implementation of myelin repair treatments. The Research Group has expanded with the addition of Sian Blake in the Spring of 2002, studying the developmental biology of Schwann cells, and Dr Luke Bennetto in late 2002, a clinical registrar exploring mechanisms of chronic disability in MS. Dr Chris Halfpenny continues his research looking at human neural stem cells and oligodendrocytes; Dr Tracey Benn is studying neural injury and Schwann cells *in vitro*; Aaron Durrant is exploring the experimental neuropathology of MS lesions. The laboratory continues to be expertly managed by Viv Down. A new and exciting development is the establishment of links with Prof. Jill Hows, exploring the potential for repair of **human adult bone marrow derived stem cells**, work set to expand during 2003.

Outside glial cell science, we also continue to be interested in the development and delivery of immune-modifying treatments. Collaborative clinical trial work with Professor David Wraith (University of Bristol Department of Pathology and Microbiology) we hope will begin during 2003, looking at novel ways developed by Professor Wraith of controlling the immune abnormalities seen in MS. The Multiple Sclerosis Group continues to be involved in the Plymouth MS Cannabis trial.

Research Activities and Interests



Cells studied include bone marrow and brain-derived stem cells. Examining MS tissue provides further opportunities for understanding myelin repair in MS.

Last but not least, our interest in integrated, patient-based MS clinical care has also seen substantial practical developments this year with the development of a local infrastructure to deliver the new *Department of Health Scheme for Disease-Modifying Treatments in MS*. With substantial financial input from the pharmaceutical industry, and with support from the local Primary Care Trusts, we have successfully established two new specialist MS Nurse posts, a clerical/administrative supporting post, and both junior and senior medical posts all dedicated to MS care and research. The **Multiple Sclerosis Centre** development in the old Stable Block on the Frenchay site, which will combine high quality co-ordinated, focused science with multi-faceted clinical and social care, also proceeds with success. Fundraising, coordinated by the *MS Nerve Centre* charity, is expected soon to pass the £1 million mark, and formal Planning Permission has now been received. Building will commence during 2003.

Other inflammatory brain diseases

Fady Joseph continues to explore clinical aspects of cerebral vasculitis and other inflammatory brain diseases in the Southwest, South Wales and in other UK centres.

Myasthenia Gravis

Dr Marguerite Hill, Consultant Senior Lecturer in Neurology, is now in the process of developing a research unit studying myasthenia gravis. The principle aim is, by better understanding this disease, to develop new treatments to control this often seriously disabling disorder. Major collaborative links with the University of Bristol Departments of Social Medicine, and of Pathology and Microbiology, are part of these developments.

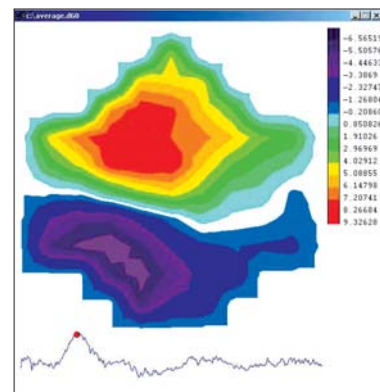
Stroke

Muscle stiffness and contractures soon after stroke are common and can hinder recovery of hand and arm function and make self-care difficult. Research has shown that muscle stiffness is not simply the direct result of neurological damage but is due in part to pathological changes in muscle due to immobility. The effectiveness of a daily stretch regime that is designed to prevent stiffness and contractures in the upper limb is being evaluated in a project funded by The Stroke Association. Over a two year period stroke patients admitted to stroke wards at North Bristol NHS Trust with impaired arm and hand movements are being invited to take part in the trial. (January 2001 - December 2003; Dr Ailie Turton with Ms Liz Britton, Physiotherapy and Dr Lindsey Dow, Care of the Elderly).

Head Injury

Head injury survivors, most of them males under 30 years of age, often experience persistent and disabling attention problems. These deficits interfere with rehabilitation and may lead to profound emotional distress, economic difficulties, and social isolation. Pharmacological treatment is still at an early stage of development. One reason for this is the lack of an objective methodology for systematically monitoring the effectiveness of different drugs. Our research aims to develop an objective procedure to improve diagnosis and to evaluate the impact of pharmacological treatments for these problems through the use of an inexpensive, rapid, non-invasive technique (event-related brain potentials). If the method proves effective, it could be made widely available through NHS clinical neurophysiology departments.

(Dr Dolores Polo and Dr Stuart Butler, with Professor David Nutt,



Psychopharmacology; Dr Danny Rogers, Neuropsychiatry; Dr John Holloway, Brain Injury Rehabilitation and Mr Brian Cummins. Supported by the Community Fund.)

Movement Disorders

Delivering high-frequency electric stimulation through tiny electrodes implanted into the brain ('Deep-Brain Stimulation' – DBS) is a reliable and efficient treatment for patients with various movement disorders. However, little is known about how this works. We are studying the neurophysiological changes induced by DBS by examining patients before, and at several different time points after implantation. By comparing neurophysiological and clinical changes we aim to provide a better understanding of the action of DBS, and of the pathophysiology of movement disorders.

(Dr Saša R Filipović in collaboration with Dr Peter Heywood, Neurology, and Dr Steven Gill, Neurosurgery.)

Hyperkinetic movement disorders, such as dystonias and dyskinesias (particularly Parkinson's disease medication-related) are sometimes difficult to treat. They are poorly understood, but some data imply impaired inhibitory mechanisms in the motor system. We are now evaluating whether repetitive low-frequency transcranial magnetic stimulation (rTMS; ≤ 1 Hz) can ameliorate impaired inhibition and induce clinical improvement.

(Dr Saša R Filipović with Dr Peter Heywood, Neurology, supported by the Parkinson's Disease Society.)

Coma

Predicting the prognosis for patients in coma can be difficult but is important, both for planning management and counselling families. Electrophysiological techniques which test the functional integrity of different systems within the brain provide additional information about the probability of recovery and possibly quality of life of survivors. Cognitive evoked potentials appear to be of particular interest as prognostic indicators. Our previous work has examined the value of such techniques in patients with traumatic brain injury. This work is now being extended to both adults and children in coma from a variety of different causes.

(Dr Stuart Butler with Drs Alex Manara and Dr Tracy Clayton, Anaesthetics; Dr Nick Kane, Clinical Neurophysiology; Drs Peta Sharples, Ravi Knight and Kayal Vijakumar, Paediatric Neurology).

Mobile Phones and the Brain.

Three years ago, in a study led by Professor Alan Preece, we reported that exposure to microwave radiation from mobile phones affected human behaviour. The findings have since been replicated and extended in six different laboratories around the world: reaction time on certain tasks is shortened and attention and memory are improved. These results were unexpected because physicists insist that the radiation should have no measurable effect on the brain at the intensity emitted by mobile phones. Although we reported no deleterious effects, our research triggered widespread concern about possibility of long terms health effects of the radiation. The government commissioned the Stewart Report on the safety of mobile phones and subsequently established the Mobile Telecommunications Health Research Programme. The programme now funds a study in which we will use electrophysiological techniques to determine how microwave radiation from mobile telecommunication systems affects brain activity.

(Dr Stuart Butler and Professor Alan Preece.)

Bristol Alzheimer's Research Group

Molecular Genetics and Brain Bank Group

Brain and DNA Bank

We have a bank where people (with or without dementia or other memory problems) have generously donated their brains, to help us further research into destructive processes in Alzheimer's and other dementias. We routinely extract and bank DNA from this brain tissue (diagnostically examined by a neuropathologist) and from blood samples from people attending our *Bristol Memory Disorders Clinic* (BMDC) who willingly consent to help further our research. To date, we have tissue from almost 700 people in our Brain Bank and DNA from a further 1000+ individuals with dementia-related illnesses from the BMDC DNA bank, as well as a small proportion of elderly undemented (control) people.

Research Programme

The main thrust of our research involves investigations for new risk factors or possible genes that may affect AD progression. We are also particularly interested, through collaboration with the BMDC and the Clinical Research Group (below), in investigating genetic factors independently influencing how people respond to pharmacological therapies. The ultimate aim of these *pharmacogenetic investigations* is to use individuals' genetic profiles to predict their risk for developing AD, how disease might progress, and how we can individualise optimal therapy. At present we use conventional DNA amplification (PCR) and enzyme digestion methods or our own ABI 310 Genetic Analyser. We are currently moving towards upgrading some of these methods.

We previously reported that a certain HLA haplotype may predispose towards AD, and we are about to publish findings that implicate a pro-inflammatory gene near HLA, *Tumour Necrosis Factor- α* , and also show the anti-inflammatory *Interleukin-10* gene also to be important in AD - all these represent risk factors independent of the well-characterised ApoE genotype. We are also soon to publish HPLC methods, and a highly specialised single cell electrophoresis (Comet) assay we have been using to test respectively for anti-oxidant status and levels of oxidative stress-induced DNA damage in people with AD.

Collaborations

Together with Professor Love, we have a number of projects underway examining neuropathological changes in dementia and their genetic influences. Two BRACE PhD studentships respectively look at the impact of Cerebral Amyloid Angiopathy in AD pathology, and how AD affects the extracellular matrix.

We are developing other close international collaborations, one with the *Centre for Genomics and Bioinformatics* at the Karolinska Institute in Sweden.

The BRACE Centre (Clinical Research Centre)

Mild cognitive impairment (MCI) appears to fall between normal ageing and AD. Not everyone with MCI develops AD, but there is an increased risk. Advances in AD therapy mean that discriminating those individuals with MCI likely to develop AD is increasingly important, particularly as optimum benefit is realised with early administration. Research is in progress to determine whether simple tests of particular cognitive functions (such as visuospatial attention) can help predict who with MCI will develop AD. In addition, we have a joint project with Professor Della Sala (University of Aberdeen), exploring other cognitive predictors of dementia. A number of studies are exploring the reliability and validity of measurement tools, particularly related to *quality of life issues*. We are also revising the Bristol Activities of Daily Living (BADLS), a scale developed at our Clinical Research Centre, in the light of feedback from its use in the clinic.

Theoretical correlates of dementia are being investigated. This research includes a survival study in collaboration with Oxford CTSU to determine long-term outcomes of people who have attended the MDC. Emotional processing of facial expressions is another project in this area.

Neonatal Neurology Group

The group is investigating the mechanisms and developing treatments for brain injury in the newborn infant.

Marianne Thoresen was the first to show that mild cooling after hypoxia can reduce brain injury in a newborn model. She has recently shown that a cooling cap, infused with cold water, can selectively cool the brain to a lower temperature than the rest of the body. Brain cooling appears to reduce the severity and duration of seizures. Another important finding is that sedation appears to be necessary for mild cooling to reduce brain damage. These laboratory studies have been running in parallel with a multicentre randomised trial of head cooling which finished recruitment (235 infants in total, including 22 in Bristol) in January 2002. Neuro-developmental assessment at 18 months is well underway. Bristol is part of the group who obtained MRC funding for a new trial of a simpler method of cooling using a mattress, starting November 2002.

Collaborating with Professor Love in Neuropathology, the group has been able to develop the first neonatal experimental model of hydrocephalus following intraventricular haemorrhage. This offers the opportunity to investigate molecular changes and therapeutic interventions. With the collaboration of neurosurgeon, Ian Pople, a

clinical trial of a radical new treatment DRIFT (Drainage, Irrigation and Fibrinolytic Therapy) has now recruited 25 babies who were developing posthaemorrhagic hydrocephalus. This shows promising results with reduced shunt surgery, disability and mortality.

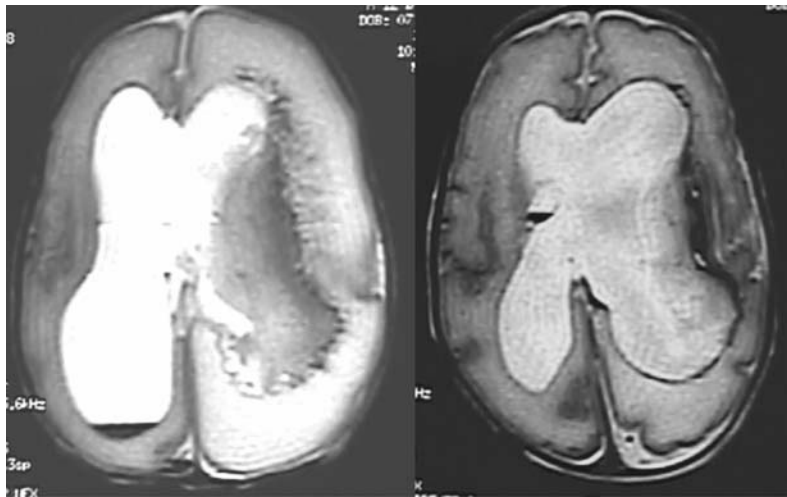


Fig 1a

Fig 1b

Fig 1a shows an MRI scan of a premature infant with hugely enlarged ventricles (white) which contain blood clot (black and grey). In Fig 1b after DRIFT, the blood is almost completely removed and the ventricles are smaller. This child survived without the need for shunt surgery.

A brain-oriented developmental intervention for premature babies, the Parent-baby interaction programme, is being evaluated in a randomised trial aimed at reducing maternal stress and depression in the short term and developmental delay in the longer term.

Neuro-epidemiology

Most of the current clinical and population-based epidemiology is focussed around movement disorders. In collaboration with Profs. Niall Quinn, Andrew Lees (Institute of Neurology and Royal Free and University College London Medical School) and others, there is an on-going programme of work testing the validity of clinical diagnostic criteria for multiple system atrophy (MSA) and progressive supranuclear palsy (PSP) with post-mortem validated cases. In addition, there is involvement with one of the steering groups looking at diagnostic criteria as part of the large European RCT (NNIPS) of riluzole for MSA and PSP (PIs Gilbert Bensimon, France, Nigel Leigh, London). Little is known about the natural history and risk factors for survival of patients with PSP. A large clinical cohort of PSP patients has been established with Dr. David Burns and colleagues (Newcastle, UK) who are being followed up both for survival and quality of life. An exploratory case control study is also being currently undertaken.

The issue of quality of life has also been paramount as part of a large European study of focal dystonias (ESDE) with Dr. Tom Warner (Royal Free and University College London Medical School). A new wave of screening of the Caerphilly cohort is currently underway to examine the determinants of healthy ageing and cognitive decline and dementia in particular with colleagues in Cardiff (Dr. John Gallagher, Tony Bayer).

Possible future work for the next few years include examining the apparent “protective effect” of smoking and Parkinson’s disease with Lars Vatten (Norway) and Brian Hurwitz (London). In addition, a new study is being planned examining risk factors related to

myasthenia gravis with Dr. Marguerite Hill (Bristol). It is hoped that over the next five years the current expertise in neuroepidemiology will be increased and a wider range of disorders will be included. It is hoped that both observational studies as well as randomised controlled trials will be mounted with interested clinical colleagues across the whole Region.

Links with the Dementia Research Group

Academic neuropathology has close collaborative links with the Frenchay Hospital-based Dementia Research Group of Professor Wilcock, with whom several joint projects have been initiated and several joint grants (from the MRC, Alzheimer's Research Trust and BRACE) are held. Current studies concern the clinical and pathological effects and genetic risk factors for the development of cerebral amyloid angiopathy in normal elderly people and in Alzheimer's disease; the mechanisms by which the three different isoforms of ApoE mediate their influence on a range of chronic degenerative and acute neurological diseases (the main focus of this research being the interrelationships between the APOE genotype, synaptic density and A β -protein deposition); the involvement of TNF- α and TGF- β in Alzheimer's disease and cerebral amyloid angiopathy; the causes and significance of extracellular matrix destruction in Alzheimer's disease; and the role of aberrant cell cycle activation in ischaemic brain damage. The MRC funding was obtained within the framework of the MRC Centre for Synaptic Plasticity (Director, Professor Graham Collingridge).

Neuropathology

Prion Diseases

This encompasses a range of projects involving human and animal prion diseases. With respect to the human prion disease, CJD, the Department of Neuropathology has participated in a Department of Health-funded national retrospective review of vCJD and related disorders. Several animal studies have been conducted in collaboration with Dr Haluk Anil and other colleagues in the Veterinary School. These studies were commissioned by MAFF and, more recently, the Food Standards Agency, in response to concerns that the use of conventional methods for commercial slaughter of cattle and sheep may risk introducing brain tissue into the blood stream, leading to contamination of the carcasses and posing a risk to public health. We have developed novel methods for measuring the entry of brain tissue into the blood stream after the use of captive bolt guns of different types, and have shown that procedures used in the UK for the slaughter of cattle and sheep risk contamination of the carcasses with brain tissue. Further funding from the Food Standards Authority is being used to confirm these observations and extend them to the analysis of the arterial circulation and edible parts of the carcass.

Most recently, the research effort in prion disease has broadened to encompass studies of murine scrapie. This work is funded by BBSRC, MRC and The Royal Society and depends on very strong collaborative links between the dept of Neuropathology and the MRC centre for Synaptic Plasticity. Their research involves detailed correlative studies, at the level of individual neurons, of the earliest electrophysiological and neuropathological changes in scrapie and in murine models of human lysosomal storage diseases.

Other collaborative research

The recent surge in academic neuroscience activity in North Bristol has seen the formation of further strong collaborative links, with the Multiple Sclerosis Group (headed by Prof Scolding) and the Division of Child Health (Prof Andrew Whitelaw and Dr Marianne Thoresen), with the implementation of several joint research projects (including a University of Bristol-funded PhD studentship concerned with glial cell biology, and a study funded by Action Research, of neonatal post-haemorrhagic ventricular dilation).

The Department continues to be actively engaged in clinical research, primarily in multidisciplinary projects with other departments within the Institute. Paediatric neuropsychology is pivotal to the projects run by Dr Peta Sharples, Consultant Paediatric Neurologist, investigating the cognitive, educational, and psychosocial outcome of children sustaining traumatic brain injury and children diagnosed with brain cancer. We have two full time research assistants employed on these studies, supervised by Renée McCarter. Ms McCarter is also investigating health related quality of life in adolescents with epilepsy.

Ms McCarter and Dr Walton have completed a study of the validity of standardised assessments of post traumatic amnesia in patients treated with opioid analgesia. The research into cognitive effects of functional surgery for Parkinson's Disease, previously carried out by Ms McCarter, is being continued by Mr Bunnage who is now commencing a project on cognition in GDNF infusion for Parkinson's Disease. He is also contributing to the Normal Pressure Hydrocephalus neurosurgical study of Richard Edwards and investigating material specific memory during Internal Carotid Sodium Amytal Wada testing. Mr Bunnage is commencing a multidisciplinary controlled trial of the efficacy of a psycho-educational programme in the management of somatisation disorder, with other members of the neuropsychiatry team at the Burden. Dr Newson is actively engaged in research for the Adult Epilepsy Surgery Programme and the BRACE Centre.

In a further project, patients with epilepsy who have undergone neurosurgical removal of the epileptic focus, performed in Bristol, are being studied to explore the effects of such surgery on memory and cognitive function. The work aims to explore the hypothesis that the successful neurosurgical treatment of their epilepsy has long term beneficial effects on cognitive function.

Neurosurgery

Mr Steve Gill and Dr Peter Heywood (Neurology) are continuing in their national and international collaborative research into the clinical effects and pathophysiological substrate of stereotactic lesioning of various parts of the basal ganglia-subthalamic complex to treat patients with Parkinson's Disease and other movement disorders: Bristol is one of the lead centres in a large national trial (funded by the MRC, Parkinson's Disease Society and Department of Health). Another ground-breaking clinical trial that is being conducted within the unit involves the continuous infusion of specific growth factors directly into parts of the brain damaged in this otherwise incurable and extremely disabling incurable neurodegenerative disease. Preliminary results, first released during an international meeting in Miami and gaining widespread attention in the lay media, are highly encouraging and the findings of longer term follow up and intense study of these patients are awaited with much excitement. In a further collaborative venture with Professor Wilcock and members of the Dementia Research Group, this approach may soon be extended to a trial of the treatment of patients with Alzheimer's disease by infusion of nerve growth factor into the ventral forebrain.



Functional neurosurgical approaches to the treatment of patients with Parkinson's disease are generating widespread interest.

Hydrocephalus and Paediatric Neurosurgery Research

Normal Pressure Hydrocephalus (NPH).

Current NPH treatment using shunt procedures carries significant morbidity. At Frenchay we have applied the technique of endoscopic choroid plexus coagulation with third ventriculostomy to treat this condition, avoiding the need for a shunt procedure. A clinical trial to evaluate the efficacy of endoscopic treatment has been commenced in collaboration with colleagues in Cleveland, Ohio (July 2002 – July 2004). We are also investigating techniques to improve diagnostic accuracy in NPH.

(IK Pople and RJ Edwards.)

Head-moulding plagiocephaly

Occipital plagiocephaly (a type of acquired skull deformity in infants) is an increasing problem, due primarily to the practice of lying sleeping infants on their back to reduce the risk of cot death. We have developed a simple, cost-effective, individualised moulding helmet to treat this condition, avoiding the need for surgical treatment.

(IKP, N. Mercer (plastic Surgery), K. Page.)

Post-haemorrhagic hydrocephalus.

The continuing collaborative work with Prof. Andrew Whitelaw, including the DRIFT study, is described above in “Neonatal Neurology”. The use of endoscopic choroid plexus coagulation as a treatment for post-haemorrhagic hydrocephalus is also under investigation. A prospective randomised controlled trial is in development.

(IKP & RJE.)

Speech & Language Therapy Research Unit

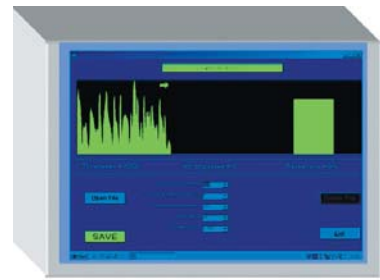
Four themes underpin the research projects that are funded within the Speech & Language Therapy Research Unit:

Development and critical examination of therapy

Three projects are key in taking forward this agenda: a follow-up study of children referred for early speech and language therapy; an observation study of therapy with children who stammer, and a study which is investigating the kind of regional network which might be needed to deliver quality services to people who stammer.

The innovative use of technology to deliver speech and language therapy

This programme of research is one of the Unit's foundations and strengths. It arises from the collaboration between Speech and Language Therapy and the faculty of Computing, Engineering and Mathematical Sciences at University of West of England, in particular the work of Dr Brian Petheram. A project, funded by the Stroke Association, to evaluate delivery by the internet of therapy for people with aphasia (language impairment following stroke) has just been completed. The results showed that the clients' word retrieval skills improved and that they achieved a high degree of independence with the software. Software is now being developed for use with people with dysarthria (disorders of speech production) and for children with speech sound difficulties.



Screen example of the Dysarthria software

The investigation of users' views of speech and language therapy

This year we have carried out a survey of computer use in speech and language therapy. The questionnaire asked about the frequency of use of therapy software and about therapists' attitudes towards computer therapy.



Screen example of the children's software

Service evaluation and planning

One of the studies completed in the unit this year tested the use of the Therapy Outcome Measure (TOM) in a benchmarking process. The results showed that access across Trusts varied by disorder, complexity and age. Number of contacts and duration of treatment also varied. The study concluded that the TOM was applicable as a benchmark tool to inform practice through comparison of outcomes for quality improvement.

Dr JRT Greene
Electroneuro-
pathology Group,
MRC Centre for
Synaptic Plasticity,
University of
Bristol

Richard Greene is the member of the ICN Academic Committee responsible for ensuring good liaison and communication between University basic neuroscience activities and the ICN. In addition, his own research activities offer valuable opportunities for collaborative research involving various ICN units.

Work in this laboratory is concerned with the biology of neuropsychiatric diseases, in particular schizophrenia, prion disease and Sandhoff's disease. Our overall aim is to identify those aspects of basic neurophysiology that malfunction in these diseases in order to facilitate a rational approach to the design of new pharmacological therapies. The experimental approach has been termed "electroneuropathology" because it places advanced electrophysiological investigations within a defined neuropathological context (see *The Electroneuropathology of Prion Disease*. Greene, J.R.T. in: *Molecular Pathology of Prion Disease* ed. Baker and Ridley, Humana Press, 2001 pp181-197). The work takes place within the MRC Centre for Synaptic Plasticity in the University School of Medical Sciences, and within the Department of Neuropathology, at Frenchay. Our work is currently funded by the BBSRC and has recently been funded by the MRC, Royal Society, and National Alliance for Research into Schizophrenia and Depression.

PET Scanning

This exciting project, initiated and driven not least by the University of Bristol Institute of Clinical Neurosciences, is now tantalisingly close to fruition. Through the development on a competitive basis of a contractual relationship with either of two major potential

suppliers, it appears highly likely that this facility will be brought to Bristol, and that building will commence during 2003.

The Institute of Neurosciences continues to be actively involved in the training of tomorrow's doctors in Bristol. Every final year medical student spends a week in the neuroscience department during their medical block, and questions on neurological problems make a frequent appearance in all parts of their final exam. Prompted by the observation that many final year students lack basic neurology skills and knowledge, we have been instrumental in ensuring that students learn about common neurological conditions and the neurological examination during their third year clinical attachment. This will hopefully provide them with the basic skills on which they can build during the last two years of their training.

This new third year curriculum is designed to accommodate the increased intake that started in September 2002, and will be delivered by all of the hospitals in and around Bristol. Delivering high quality teaching to large numbers of students will be quite a challenge. We have started to explore Web-based teaching and assessment and are keen on developing interactive learning media such as CD-ROMs and videos. Using actors to develop history taking and counselling skills is extremely valuable, both at the under- and postgraduate level. However, ultimately nothing can replace the experience of talking to real patients and so much of our teaching remains ward and clinic based. We are extremely lucky to have a number of clinicians within the department who are happy to commit their valuable time to medical student teaching.

Undergraduate Education in Clinical Neurosciences

The ICN Library

The Neurosciences Library provides a library and information service to clinical, research staff and students, to support patient care, teaching and learning, continuing education and research. It is a regional specialist resource with 75 current journal titles mostly on neurosciences subjects. Electronic links have been established with the University of Bristol and NHS networks, providing fast access to world-wide information resources. The provision of IT has been accompanied by increased visitor number, and 24 hour access has been established for senior staff. A web page will be developed during 2003.

In 2001, a lunchtime open viewing of the library was well-attended; the library was also much visited during the *Burden Centre Open Day*. Feedback was encouraging and extremely positive.

Medical students have particularly valued access to the university network. A new intake of 5th year students is inducted to the library each week, and make good use of library resources. A resource sheet of electronic information sources tailored to the neurosciences has been produced, to help users navigate their way around the vast array of information sources available. The library continues to support the Neurology Journal Club.

The substantial amount of clinical, research and scientific activity taking place within the neurosciences is reflected in statistics of library use, and in the extensive ICN bibliography which is collected, coordinated and maintained by the Neurosciences Librarian, and at the end of this report.



The Journal Club in action

New journal titles added to stock since the last annual report are:- Journal of Neurology, Journal of Sleep Research, Lancet Neurology, Practical Neurology, Sleep and Sleep Medicine Reviews. A journals review is currently taking place to rationalise titles, where possible avoiding duplication with the University of Bristol. It is anticipated that access to more electronic titles will be required in the future.

The Neurosciences Library can be contacted at the Burden Centre, Frenchay Hospital, Bristol BS16 1JB. Tel. 0117 9701212 Ext. 2942. E-mail jane.sweetland@north-bristol.swest.nhs.uk

ICN Research Day

The second ICN Research day took place in December 2002. In contrast with the first event last year, the programme on this occasion filled a whole day. Individuals from research-active units throughout the ICN delivered brief presentations on their own projects. Again, the success of the event was manifest not only in the talks themselves, which strikingly emphasised the increasing breadth and depth of research activities within the ICN, but in the enormously valuable inter-group scientific dialogue and exchange of views and of expertise. A further, whole day, event is planned for 2003; abstracts from the talks will be posted on the website which we hope to be available by then.

ICN RESEARCH DAY			
DECEMBER 3RD 2002, POSTGRADUATE CENTRE, FRENCHAY HOSPITAL			
9.25-9.30	Neil Scolding		Introduction & welcome
9.30-9.40	Andrew Curran	Paediatric Neurology	Family functions & maternal emotional in post-traumatic brain injury
health			
9.45-9.55	Ailie Turton	BNI	Sensorimotor integration - proprioception and pain
10.00-10.10	Corinne Dobinson	SLTRU	Role of computers in independent practice for people with dysarthria
10.15-10.25	Shoba Cherian	Neonatal Neurology & Neuropathology	Neonatal hydrocephalus & ventricular haemorrhage: a rodent model.
10.30-10.40	Andrea Tales	Care of the Elderly	Attentional Function in Alzheimer's disease
10.45-10.55	Sasa Filipovic	BNI	Title TBC
11.00-11.30	COFFEE		
11.30-11.40	Kate Chalmers	Neuropathology & John James Lab	The Pathogenic role of cerebral amyloid angiopathy in Alzheimer's disease
11.45-11.55	Kayal Vijaykumar	Paediatric Neurology	Neurological outcome in children with meningococcal disease.
12.00-12.10	James Tooley	Neonatal Neurology	Therapeutic Hypothermia
12.15-12.25	Fady Joseph		Academic Neurology SLE and the Nervous System
12.30-12.40	Zoe Chiti	Anatomy	The hippocampus in prion disease
12.45-12.55	Biju Hammeed	Paediatric Neurology	Steroids, Receptors and Neurotrophic responses in traumatic Brain Injury
13.00-14.00	LUNCH		
14.00-14.10	Ravi Knight	Paediatric Neurology	Title TBC
14.15-14.25	Sue Tyler	Dementia RG*	BACE and TACE in Alzheimer's disease
14.30-14.40	Julia Wade	SLTRU	Use of voice recognition software by people with dysphasia
14.45-14.55	Chris Halfpenny	Glial Cell Labs.	Oligodendrocyte Progenitors are Resistant to Anti-Inflammatory Drugs
15.00-15.10	Anthony Penn	Paediatric Neurology	The effects of childhood brain tumours on the child and family
15.15-15.45	TEA		
15.45-15.55	Dolores Polo	BNI	ERPs for the evaluation of attention difficulties after head injury
16.00-16.10	Martin Thornton	Laryngeal RG*	Adhesion molecules in regenerating peripheral and cranial nerves
16.15-16.25	Helen Miller	Paediatric Neurology	Early Psychological Response to Head Injury in Children
16.30-16.40	Nic Patel	Neurosurgery	GDNF infusion in Parkinson's Disease
16.45			CLOSE *Research Group



UNIVERSITY OF BRISTOL



BURDEN NEUROLOGICAL INSTITUTE

North Bristol NHS Trust

ICN Publications 2002

We have this year not included presentations, abstracts, etc

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