

# **Raised Human Brain Temperature Good or Bad After Traumatic Brain Injury?**

## **Symposium and Workshop**

Wednesday 26<sup>th</sup> November 2008

Chancellors Hotel and Conference Centre



School of Translational Medicine  
Brain injury Research Group



# PROGRAMME

8.30-9.00	<b>Registration and Coffee Griffiths Room</b>
9:00	<b>Welcome</b> Professor Chris Griffiths: Associate Dean for Research Faculty of Medical and Human Sciences, University of Manchester
9.00-9.10	<b>Morning - Keynote Lectures in the Marquis Room</b> Chair- Dr Pippa Tyrrell, Research Group Lead, Clinical Neurosciences
09.10-09.40	Introduction- The Role of Temperature in the Damaged Brain Dr Charmaine Childs, University of Manchester, UK
09.40-10.00	Is Therapeutic Hypothermia a Double Edge Sword? Professor Tadeusz Wieloch, Wallenburg Neuroscience Centre Lund, Sweden
10.00-10.30	Temperature as a marker of secondary brain damage: Results from IMPACT Dr Fiona Lecky, Research Director, TARN UK
10.30-11.00	What are the possibilities for accurate (clinical) temperature measurement? Professor Graham Machin, National Physical Laboratory, UK
11.00-11.20	<b>Coffee Break and Trade Exhibition Griffiths Room</b>
11.20-11.40	New approaches to temperature management after TBI Ms Bridget Harris, University of Edinburgh, UK
11.40-12.10	Pyrexia: how does it influence brain oxygenation and chemistry? Professor Nino Stocchetti, University of Milan, Italy
12.10-12.40	Brain temperature and outcome after TBI: evidence from bench to bedside Dr Charmaine Childs, University of Manchester, UK
12.40-13.45	<b>Lunch and Trade Exhibition Griffiths Room</b> <b>AFTERNOON Marquis Room</b> Roundtable Workshop: Towards an evidence-based strategy for management of early pyrexia after TBI Facilitator: Ms Denise Fieldhouse, Staff Development Advisor Transcriptions: Mrs Sharon Hulme, Ms. Danni Kirk, Ms Anna McGlone, Mrs Geraldine Coombs
13.45-14:15	Q: 1. Measurement or surrogate for brain temperature What recommendations for the future?
14:15-14:45	Q: 2. Cooling after TBI: Panacea or Prescription?
14:45-15.00	<b>Coffee Break Griffiths Room</b>
15.00-15.45	<b>Feedback on Questions:</b> Facilitator: Ms Denise Fieldhouse
15.45-16.30	Is there consensus to support new research into the effect of raised temperature on short and long-term outcome: what are the key messages for a consensus document? Are we ready for a definitive trial?

## CLOSING REMARKS

## Conference Organiser

Dr Charmaine Childs  
University of Manchester

Dear Delegate

I am delighted to welcome you to this first 'Human Brain Temperature' conference and workshop.

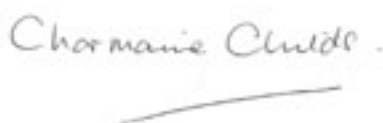
It is now 12 years since The World Health Organisation (WHO) report that road traffic crash-related injuries, a common cause of severe brain injury, were set to rise from 9<sup>th</sup> to 3<sup>rd</sup> place in world disease-burden ranking. Treatment to improve the outcome of predominantly young TBI patients has, at its roots, the need for robust information on the mechanisms involved in secondary brain damage. In this regard temperature has been shown to be a major factor in neuronal survival in the setting of cerebral ischaemia in rodents: high temperature increasing, and low temperature reducing, risk of brain damage.

In patients, the benefits of treatment of pyrexia in terms of improved outcome remain speculative. We are still uncertain about whether raised temperature is an adaptive response to trauma which may confer elements of host protection or whether it is harmful and leads to a poor outcome. If there are exceptions to either case, we are as yet, unclear about how to identify these low/high risk patients.

The lectures this morning set the scene for what I anticipate will be a lively afternoon workshop. Our objective for the day is to work towards producing a brief consensus statement to identify areas for future research, particularly with regard to obtaining accurate measures of brain temperature and how we might strive towards development of an evidence-based approach to pyrexia which we can be confident is appropriate and risk-free for the patient.

I would like to take this opportunity to thank the speakers for travelling to Manchester to present their research and for sharing their expertise with us. I am particularly grateful to all the participants for joining us to help advance the development of a rational approach to measurement and management of temperature in brain injured patients.

Finally, I would like to thank all the sponsors for appreciating and supporting this venture.



Charmaine Childs

## Welcome Address

Professor Chris Griffiths  
Associate Dean for Research  
Faculty of Medical and Human Sciences  
University of Manchester

## Lecture Session Chair

Dr Pippa Tyrrell  
Senior Lecturer and Honorary Consultant  
Clinical Neurosciences Group Research Lead  
School of Translational Medicine  
University of Manchester

## Facilitator Round Table Session

Mrs Denise Fieldhouse  
Staff Development Advisor,  
Faculty of Medical and Human Sciences  
University of Manchester

# The Role of Temperature in the Damaged Brain

Dr Charmaine Childs

Senior Research Fellow

Brain Injury Research Group

University of Manchester

Charmaine Childs obtained her first degree in 1980 (University of Manchester) an M. Phil in 1986 (University of Nottingham) and a PhD in 1989 from the University of Manchester. Her early research identified the effect of severe burn injury on body temperature and the mechanisms involved in the acute phase changes in plasma and tissue cytokines, heat content, heat loss and metabolism. After a period in clinical practice and as a lecturer, Charmaine returned to full-time research to continue her work in burn trauma. Her postdoctoral research was followed by her appointment to the Medical Research Council Trauma Unit in Manchester. Here Charmaine led a research programme investigating the human thermoregulatory and metabolic response to trauma. Charmaine's research in paediatric burns was recognised internationally, winning five research prizes and an invitation to Chair the European Burns Association Research Committee.

Charmaine has now focused her research to the brain. Studies involve the investigation and use of new methods for measurement and validation of invasive and non-invasive (imaging) techniques for brain temperature measurement. More recent studies are elucidating the contribution of biomarkers and altered brain temperature to long-term outcome after severe brain injury.

## Abstract

In animals, the local and systemic responses to inflammation and infection is a rise in body temperature. Fever, with its long evolutionary history confers benefit for the host in terms of bacterial killing and increased immunity. Numerous studies have been conducted in invertebrates, fish and mammals-the survival benefit of fever is evident. It is clear also that mortality increases if the febrile response is prevented or blocked, either by cold exposure or by the use of antipyretic drugs.

In patients, fever is common after inflammation and trauma and is widely considered to have a beneficial role in 'fighting' infection. However, if the injury leads to tissue damage in the brain, it is thought that (ischaemic) brain cells have reduced tolerance to heat. Studies in animals show that hypothermia preserves, and hyperthermia accelerates ischaemic tissue. Whilst there is evidence to support the case for therapeutic neuroprotection in brain ischaemia (cardiac arrest, neonatal hypoxic ischaemia, stroke) the benefits of hypothermia remains speculative in patients with brain trauma. On balance, current opinion supports the view that fever is likely to be of biological benefit after systemic trauma whereas in brain ischaemia, any protective benefits are outweighed by the presumed increased vulnerability of CNS tissue to damage by heat.

The uncertainty about the role of fever after brain trauma presents a dilemma for the clinician; how can appropriate, evidence-based, decisions be made when there is a lack of robust data to underpin practice about which patients should be a priority for treatment of pyrexia and which patients are at low risk of temperature-related secondary damage? In this two part presentation the role of brain temperature on short and longer term effects on outcome after traumatic brain injury will be explored.



# Is Therapeutic Hypothermia a Double Edge Sword?

Professor Tadeusz Wieloch  
Professor of Neurobiology  
Wallenberg Neuroscience Centre  
Lund Sweden

Professor Tadeusz Wieloch, PhD, was born 1950 in Lund, Sweden. He graduated in 1974 from Lund University and received a PhD in 1981 from the same University. Shortly thereafter he became Assistant Professor at Lund University, at the Laboratory for Experimental Brain Research at that time headed by Professor Bo Siesjö, and became Associate Professor at Lund University in 1985. He became Professor of Neurobiology in 1993 at Lund University, and moved to the Wallenberg Neuroscience Center in Lund 1996.

Since 1981 Dr. Wieloch has been investigating the mechanisms of brain damage following cerebral ischaemia and hypoglycaemia, including mechanisms of brain protection by hypothermia and ischaemic preconditioning, and more recently mechanisms of functional recovery of the brain after stroke. He has published 150 articles in this area of research. He recognized early on the potential involvement of glutamate receptors in acute brain injury and was the first to demonstrate this in a model of hypoglycaemic brain damage in the rat. He has made fundamental discoveries on cell signalling following experimental stroke, among others the involvement of protein kinase C, CaM kinase II and the MAPKinase systems. He also demonstrated that blocking the mitochondrial permeability transition pore with cyclosporinA protected the brain against hypoglycemic brain injury. Furthermore, his group also identified mitochondrial uncoupling protein 2 as a potent inducible neuroprotectant using massive gene profiling. Using similar techniques his group have identified the sigma -1 receptor as an important mediator of brain plasticity following brain damage, and also identified a compound that can potentially be used for treating stroke patients as late as 2 days after stroke onset.

He has obtained several awards, among others The Fernström award for young scientists. He has been presenting at symposia at major Neuroscience meetings. He is an avid educator, teaches medical students in neurobiology, and 22 PhD-thesis have been presented from his research group.

## Abstract

Neuroprotection by hypothermia in cardiac arrest patients, is currently the only neuroprotective treatment paradigm that has successfully been translated from bench to bedside. It is now considered as treatment after neonatal asphyxia, brain trauma, cardiac ischaemia and stroke.

From experimental ischaemia conducted mainly in rats, the mechanisms of neuroprotection by hypothermia appears to be multifactorial and depend on the severity of the insult, the depths of hypothermia and time of induction following brain ischemia and duration of hypothermia.

The pathomechanisms of cerebral ischaemia are complex, and many act as a 'double-edged sword', with both beneficial and deleterious effect: Glutamate and calcium ions are major players in excitotoxicity, but are essential for normal brain function and a key driving force of reorganization and synaptogenesis after injury. Nitric oxide (NO) derived from endothelia may increase blood flow while neuronal and inducible NO synthase (NOS) may contribute to the formation of oxidants and free radicals. Inflammation exacerbates ischaemic injury, but is necessary for regeneration and repair. Formation of a glial scar may contain the lesion and impede its progression, but at the same time produces a barrier for axonal sprouting. These facts raise the issue of whether or not therapeutic hypothermia is only beneficial? Could hypothermia be protective early during recovery but later impede recovery?



# Temperature as a Marker of Secondary Brain Damage

## Results From IMPACT

Dr Fiona Lecky  
Senior Lecturer and Honorary Consultant  
Research Director  
UK Trauma Audit Research Network (TARN)  
University of Manchester

Fiona Lecky is a Senior Lecturer in Emergency Medicine and Honorary Consultant at Salford Royal NHS Foundation Trust in Salford. Fiona’s role also includes that of Research Director of the Trauma Audit and Research Network ( [www.tarn.ac.uk](http://www.tarn.ac.uk) ).

Fiona trained both as an undergraduate and Emergency Physician in the North West. During the latter period she received a Wellcome Fellowship in Clinical Epidemiology which enabled her to look at clinical and biochemical matters of shock in major injury for her PhD.

Recent publications include those looking at trends in trauma outcome and clinical effectiveness in trauma care with a particular focus on head injury. A Lancet publication has harnessed the power of the TARN database in collaboration with neurosurgeons to demonstrate that specialist care is crucial in optimising outcome in severe head injury.

## NOTES

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# What Are the Possibilities for Accurate (Clinical) Temperature Measurement?

Professor Graham Machin  
Head of Temperature Standards  
National Physical Laboratory

Graham Machin has worked at NPL in temperature measurement for nearly 20 years. He was instrumental in establishing world-class facilities at NPL for realising and disseminating ITS-90 by non-contact thermometry from  $-40\text{ }^{\circ}\text{C}$  to  $\sim 3000\text{ }^{\circ}\text{C}$ .

His current research interests are medical thermometry, high temperature thermometry, both non-contact and contact, acoustic thermometry, the kelvin redefinition via the Boltzmann constant and quantitative thermal imaging. He has published over 60 papers on many different aspects of temperature measurement.

He currently represents NPL at the CCT (Comité Consultatif de Thermométrie), Euramet TC Thermometry, chairs CCT-WG5 (Radiation thermometry) and contributes to the CCT task groups on the kelvin redefinition and mise-en-pratique.

He is a Fellow of the Institute of Physics and visiting Professorship at the University of Glamorgan (Medical Thermal Imaging) and the University of Valladolid (Temperature Standards).

## Abstract

This talk will focus on some of the recent developments that have taken place in the practice of medical thermometry. Beginning with a brief outline of how to establish reliable temperature measurements and instrument calibration the following areas of medical thermometry will be addressed:

- Validation studies of in-situ probes for brain temperature measurement
- Validation of internal temperature measurement studies based on MRI spectroscopy
- The establishment of techniques for the calibration and validation of ear thermometers
- Improving the practice of quantitative clinical thermal imaging

One of the recurrent themes of this talk will be the deployment of fixed-points, that melt at very precise temperatures, as secondary reference temperature standards for medical thermometry.



## Irwin Mitchell Solicitors



Irwin Mitchell provides legal services nationally and is one of the most highly regarded personal injury practices in the country. We have offices in 7 major cities in the UK and employ in excess of 2,300 people. Currently we are the fourth largest UK law firm (by number of legal advisors) and National Law Firm of the Year 2007 (The Lawyer). Our stated vision for the next three years is 'to exceed every client's expectations' and for our injured and disabled clients, this translates to helping wherever we can to optimise their quality of life, not simply focusing upon the litigation. Earlier this year, Irwin Mitchell won the Rehabilitation Initiative of the Year - Claimant Solicitor (Post Magazine Rehabilitation First Awards), in recognition of the holistic approach we adopt to client care and rehabilitation

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Our technology and materials expertise has seen us develop from our core TUBINGS business through the business unit COMPONENTS into a systems supplier for sub-assemblies and catheter systems to complete assemblies in selected market segments.

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## Lambda Photometrics



Lambda Photometrics Ltd. are the UK Distributor for LumaSense Inc. LumaSense manufacture a range of Fibre Optic Temperature Measuring Equipment for use in Microwave and RF environments where conventional Temperature Measuring Equipment is not suitable.



LumaSense has been a leader in the field of temperature measurement and thermal imaging for more than 30 years. The company's fiber optic Luxtron family of products are used by thousands of customers around the world. Fluoroptic<sup>®</sup> optical sensor technology is based on the fluorescence decay time of a special thermo-sensitive phosphorescent (phosphor) sensor, located at the end of a fiber optic cable.













# Round Table Discussions

## Facilitator: Denise Fieldhouse

Staff Development Advisor,  
Faculty of Medical and Human Sciences  
University of Manchester

Denise Fieldhouse is a staff development advisor working in the University Staff Training and Development Unit. Denise has over 17 years experience in human resource management/development and has spent the last 7 years at the University of Manchester. As the link person for the Faculty of Medical and Human Sciences Denise regularly facilitates away days, team building sessions, psychometric testing, coaching and training sessions. She recently graduated with a MSc in the Psychology of work and is particularly interested in equality and diversity issues

## For Discussion:

1 Measurement or Surrogate for Brain temperature. What recommendations for the future?

2 Cooling after TBI-Panacea or Prescription?

# Workshop Seating Plan

## Table 1

Geraldine Coombs

(Transcribing)

Steve Hopkins

Richard Protheroe

Nino Stocchetti

Christos Tolias

Chris Whitehead

## Table 2

Sharon Hulme

(Transcribing)

Ian Geraghty

Bridget Harris

Raphael Sacho

Martin Smith

Pippa Tyrrell

## Table 3

Danni Kirk

(Transcribing)

Paul Dark

Arun Gupta

Andy King

Graham Machin

## Table 4

Anna McGlone

(Transcribing)

Iain Chambers

Nicola Johnston

Gareth Thomas

Andy Vail

Tadeusz Wieloch

## Participants

Name	Title	Institute
Dr Iain Chambers	Director of Medical Physics	The James Cook University Hospital, Middlesbrough, UK.
Dr Charmaine Childs	Senior Research Fellow Honorary Senior Lecturer, Brain Injury Research Group	University of Manchester and Salford Royal Hospitals NHS Foundation Trust, UK
Mr Grahame Codd	Managing Partner, Regional Managing Partner for the North-West Specialist Area: Brain injury and spinal injury cases	Irwin Mitchell Solicitors Manchester UK
Ms Geraldine Coombs	Associate Solicitor	Irwin Mitchell Solicitors Manchester UK
Dr Paul Dark	Senior Lecturer Honorary Consultant Intensive Care Medicine	University of Manchester/ Salford Royal Hospitals NHS Foundation Trust, UK
Mrs Denise Fieldhouse	Staff Development Advisor, Faculty of Medical and Human Sciences	University of Manchester, UK
Dr Ian Geraghty	Consultant in Intensive Care Medicine	Salford Royal Hospitals NHS Foundation Trust, UK
Professor Chris Griffiths	Associate Dean for Research, Faculty of Medical and Human Sciences	University of Manchester, UK
Dr Arun Gupta	Director of Neurosciences, Critical Care Unit	Addenbrooke's Hospital, Cambridge University Hospitals NHS Foundation Trust
Mrs Bridget Harris	Honorary Research Fellow, Clinical and Surgical Sciences	University of Edinburgh, UK
Dr Steve Hopkins	Honorary Reader, Brain Injury Research Group	Salford Royal Hospitals NHS Foundation Trust, UK
Mrs Sharon Hulme	Research Nurse, Brain Injury Research Group	University of Manchester, UK
Miss Nicola Johnston	Research Fellow in Neurosurgery	Salford Royal Hospitals NHS Foundation Trust, UK
Mr Andrew King	Honorary Lecturer Clinical Director and Consultant Department of Neurosurgery	Salford Royal Hospitals NHS Foundation Trust, UK
Ms Danni Kirk	Undergraduate Medical Student Year 5	University of Manchester, UK
Dr Fiona Lecky	Senior Lecturer in Emergency Medicine/ Honorary Consultant	University of Manchester and Salford Royal Hospitals NHS Foundation Trust, UK

Name	Title	Institute
Dr Andrew Levick	Principal Research Scientist	National Physical Laboratory, UK
Professor Graham Machin	Head of Temperature Standards, Temperature Group	National Physical Laboratory, UK
Ms. Anna McGlone	Undergraduate Medical Student Year 5	University of Manchester, UK
Dr Richard Protheroe	Consultant in Intensive Care Medicine	Salford Royal Hospitals Foundation Trust, UK
Mr Timothy Rainey	Research Technician, Brain Injury Research Group	University of Manchester, UK
Mr. Raphael Sacho	Research Fellow in Neurosurgery	Salford Royal Hospitals NHS Foundation Trust, UK
Dr Martin Smith	Director Neuro-Monitoring Research Group, Department of Neuroanaesthesia	University College London, UK
Professor Nino Stocchetti	Professor, Institute of Anaesthesiology and Intensive Care	University of Milan, Italy
Dr Gareth Thomas	Consultant in Intensive Care Medicine	Salford Royal Hospitals NHS Foundation Trust, UK
Mr Christos Toliás	Consultant Neurosurgeon and Honorary Senior Lecturer Academic Neurosurgery Unit	King's College London, UK
Dr Pippa Tyrrell	Senior Lecturer/Honorary Consultant. Research Group lead Clinical Neurosciences Group	University of Manchester and Salford Royal Hospitals NHS Foundation Trust, UK
Mr Andy Vail	Senior lecturer, Health Methodology Research Group	University of Manchester, UK
Ms Elena Vescovo	Doctoral Student, Imaging Science	University of Manchester, UK.
Dr Chris Whitehead	Clinical Director, Critical Care Department	The Walton Centre for Neurology & Neurosurgery, UK
Professor Tadeusz Wieloch	Professor of Neurobiology	Wallenburg Neuroscience Centre, Lund, Sweden

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We would like to thank our sponsors for their  
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