

# Ask the Experts Session

**Maritim Hotel, Berlin**  
**6<sup>th</sup> December 2009**

**SPEAKER: Pamela Shaw MD**

## **BIOGRAPHY:**

Professor Pam Shaw is Professor of Neurology, University of Sheffield, Consultant Neurologist, Royal Hallamshire Hospital, Sheffield and Director of the Sheffield Care and Research Centre for Motor Neuron Disorders and the Sheffield Institute of Translational Neuroscience (SITraN). She is Associate Director, Chair of the Motor Neurone Disease Clinical Studies Group and Experimental Medicine Lead for the UK Dementia and Neurodegenerative Diseases Clinical Research Network (DeNDRoN). She has since 1991 led a major multidisciplinary programme of research investigating genetic, molecular and neurochemical factors underlying neurodegenerative disorders of the human motor system and evaluating potential neuroprotective agents and improvements in symptomatic management in the clinic.

Awards made to Professor Shaw include for her work on MND include: the Association of British Neurologists Sir Charles Symonds Prize (1991); American Academy of Neurology Sheila Essey Award (2001); elected Fellowship of the American Neurological Association (2004); the UK Royal College of Physicians Jean Hunter Prize (2006); elected Fellowship of the Academy of Medical Sciences 2007.

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**SPEAKER: Pamela Shaw**

**TITLE OF PRESENTATION: Pathomechanisms of ALS**

**ABSTRACT:**

MND with a prevalence of 6-8 per 100,000 is a rapidly progressive neurodegenerative condition in which cell death of motor neurons causes loss of the connection between the central nervous system and the voluntary muscles controlling limb, bulbar and respiratory function. MND is a group of diseases rather than a single disease entity. This has major implications for testing new therapies and the heterogeneity of disease may be one important reason why most clinical trials of potential neuroprotective therapies have so far proved unsuccessful. We have greatest understanding of disease mechanisms in the subtype of MND caused by Cu/Zn superoxide dismutase (SOD1) mutations, but these account for less than 20% of familial cases and approximately 2% of MND patients as a whole. Other genes identified as causing MND eg VAPB, SETX, dynactin and alsin, represent relatively rare variants. TDP-43 and FUS/TLS mutations have recently been identified as a cause of familial and some cases of sporadic ALS and further investigation of the biology of the encoded proteins in health and disease is of crucial importance, particularly as the TDP-43 protein forms aggregates in motor neurons from sporadic MND patients. Both genetic and environmental factors are likely to contribute to the pathogenesis of sporadic MND.

This presentation will cover several areas where our knowledge of the mechanisms of motor neuron injury in ALS/MND has advanced including: 1. Current knowledge of environmental factors associated with ALS/MND; 2. New insights from genetic factors which are associated with familial and sporadic disease, highlighting the potential role of disturbance of RNA processing in motor neuron injury ; 3. The importance of cross-communication between motor neurons and the cells and tissues they interact with including glial cells in the nervous system; 4. The importance of the health of the distal axon which is the part of the motor neuron which connects with the muscles.

The presentation will end with consideration of how the tools of science can be harnessed to further advance our knowledge of the pathophysiological mechanisms of ALS/MND which is crucial for the development of more effective neuroprotective therapies.

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**SPEAKER: Walter G. Bradley DM FRCP**

**BIOGRAPHY:**

**Walter G. Bradley DM, FRCP** went to college and medical school at Oxford University, graduating in 1963. He trained in neurology and was Professor of Experimental Neurology in the University of Newcastle upon Tyne 1974-1977. He was Vice Chairman of the Department of Neurology at Tufts-New England Medical Center 1977-1982; Chairman of the Department of Neurology in the University of Vermont 1982-1990; and Chairman of the Department of Neurology of the University of Miami from 1990 to 2007, where he is now Professor and Chairman Emeritus. He is a Fellow of the Royal College of Physicians and Board Certified in Neurology and Psychiatry. He has authored 28 books, including “Treating the Brain: What the best doctors know”, a book about neurological diseases for the lay public, published by Dana Press in October 2009; over 200 peer-reviewed articles; and more than 120 book chapters, invited reviews and electronic publications. He was founding editor of “Muscle and Nerve” 1977-1986 and Editor of the Yearbook of Neurology and Neurosurgery from 1993-2000. He is lead editor of the best-selling textbook of neurology, “Neurology in Clinical Practice”, published by Elsevier. He has cared for patients with amyotrophic lateral sclerosis and done research to find the cause and cure of the condition for more than 40 years. He is Director Emeritus of the Kessenich Family MDA ALS Center in the University of Miami.

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**SPEAKER:** Walter G. Bradley DM FRCP

**TITLE OF PRESENTATION:** Environmental toxins as the cause of sporadic ALS.

**ABSTRACT:**

Research indicated that the Guam form of endemic ALS (which includes Parkinsonism-Dementia, ALS/PDC) is strongly associated with exposure to a non-protein amino acid, BMAA, produced by cyanobacteria in specialized roots of the cycad and concentrated in its seeds that are the source of the Chamorro's flour and are also eaten by animals that are major food sources for the islanders. BMAA is found in the protein fraction of brains of patients dying with ALS/PDC at concentrations sufficient to produce chronic neurotoxicity, but not in control brains. Recent research has found BMAA in the brains of patients dying with ALS, Alzheimer's and Parkinson's diseases, but not in control brains, including patients dying with Huntington's disease. Cyanobacteria producing BMAA and other neurotoxins are ubiquitous and may be responsible for sporadic ALS worldwide, and for the increased incidence of ALS in US troops deployed in the first Gulf War, as well as clusters of ALS cases in the Kii peninsula of Japan and lakes in New England that have cyanobacterial blooms. Until we know what causes ALS it will not be possible to develop ways to prevent and treat it. This research offers such possibilities.

Until we have an effective cure, it is essential that patients with ALS be provided with symptomatic treatment. This includes: assisting communication as speaking deteriorates; assisting swallowing, maintaining nutrition with parenteral feeding, and reducing sialorrhea as bulbar function deteriorates; assisting respiration with nocturnal and eventually 24-hour NIPPV as respiratory function deteriorates; maintaining mobility and upper limb function with therapy, aids and appliances; providing treatment for pseudobulbar emotional lability; providing psychological support and medications as needed for depression in patients and family members; assisting with interface with the healthcare system; providing counselling about end of life issues leading either to appropriately timed tracheostomy and ventilator support or palliative care, including hospice care. Participation in clinical therapeutic trials and other ALS research is of great benefit to maintaining patient and family morale. A multidisciplinary team of caring specialists provides the best milieu for delivering this symptomatic treatment.

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**SPEAKER:**            **Albert Christian Ludolph**

**BIOGRAPHY:**

1979 - 1984	Resident, Board Neurology and Psychiatry (Department of Neurology and Psychiatry, University of Münster FRG) (Prof. G. Brune, Prof. R. Tölle)
1984 - 1985	Stipend, Deutsche Forschungsgemeinschaft: Institute of Neurotoxicology, Albert Einstein College of Medicine, Bronx, New York(Prof. P.S. Spencer, Prof. H.H. Schaumburg)
1985 - 1989	Staff, Department of Neurology, University of Münster (Prof. G. Brune)
1987	Habilitation, Faculty of Medicine, University of Münster, C2 Professor of Neurology
1990 - 1992	Staff Scientist, Visiting Assoc. Prof. Center for Research on Occupational and Environmental Toxicology, Portland (Oregon)
1992	Staff, Department of Epileptology, University of Bonn (Prof. C.E. Elger)
1993 - 1996	C3 Professor of Neurology, Vice Chairman, Department of Neurology, Humboldt University Berlin (Prof. K.-M. Einhäupl)
1996	C4 Professor of Neurology, Chair, Department of Neurology, University of Ulm
2003 -	Chair (elected) Academic Neuroscience Center, University of Ulm
2005 – 2009	Deputy Chair and Chair (elected), European ALS-MND-Group
2009 -	Chair (elected), World Federation of Neurology, Research Group on ALS/MND
1999 -	Advisor German Charcot-Foundation (ALS)
2003 -	Chair (elected) Academic Neuroscience Center, University of Ulm
2005 – 2009	Deputy Chair and Chair (elected), European ALS-MND-Group
2008 -	Chair Scientific Council Deutsche Gesellschaft für Muskelkranke
2009 -	Deputy Chair Word Federation of Neurology ALS Research Group

# Ask the Experts Session

Maritim Hotel, Berlin  
6<sup>th</sup> December 2009

**SPEAKER:** Albert C. Ludolph

## **TITLE OF PRESENTATION: Genetic animal models and future treatment of ALS**

### **ABSTRACT:**

Approaches to treatment for ALS can be separated into pharmacological and symptomatic ones. The only current pharmaceutical approach to ALS-treatment is restricted to riluzole; it is important to state that riluzole treatment is largely underestimated with regard to its effect. This is particularly true if the effect of this drug is compared with – “breakthrough drugs” in fields like oncology.

Symptomatic treatment of ALS can be greatly improved in the future. Major issues under discussions are non-invasive ventilation (when to start, which mask?) and nutritional interventions (how? lipid rich? enteral interventions?....)

For other future treatments I see the following approaches:

1. Etiology related – treatment forms.
2. Pathogenesis – related treatment forms.
3. Prevention.

Ad 1: Since we have only limited access to the etiology of ALS, these approaches will be only done in a quantitatively less important number of patients. This is so, since monogenetic modes of inheritance are only a minor etiologic factor in ALS. However, these approaches must be done; they could be done by lowering transcription and translation rates of potentially toxic gene products (for example of the SOD1-gene).

Ad 2: Since ALS was defined by Charcot as a syndrome, this approach seems to be the currently most promising. However, in the recent past evaluation of pathogenesis-based approaches was done in transgenic rodent models only. Translational research was quite unsuccessful and it need to be improve. Improvement could be done by improving methods of evaluation, development of biomarkers, including pharmacological methods of assessment, and the use of models other then rodents. Also improvement of methods of target validation could be a major step forward.

Ad 3: If ALS, like every other neurodegenerative disease, has a preclinical period which can be defined by molecular means, then prevention is in principle possible. Important requisites for progress are the following:

- a) a staging of the preclinical period
- b) development of biomarkers in models (mice) and men which serve as endpoints for preclinical and clinical studies. First steps are taken and will be demonstrated.

In conclusion, a systematic approach to future treatments will clearly install the greatly needed therapies of the future for ALS.

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**SPEAKER:           Professor Thomas Meyer**

**BIOGRAPHY:**

Thomas Meyer is Professor of Neurology and chief of the ALS service at the Charité University Hospital in Berlin. In 1994-1994, he was a research fellow in the Department of Neurology of the Mount Sinai School of Medicine in New York, USA. He graduated from Medical School of the Humboldt University of Berlin in 1996 and became resident in neurology at the university hospital in Ulm, Germany. While at the university of Ulm with Albert Ludolph, he worked on the original cloning of human glutamate transporters and conducted the first mutation screenings of glutamate transporter genes in ALS patients. Dr. Meyer came back to Berlin and joined the faculty at the Charité in 2002, where he founded a multidisciplinary service for patients with ALS and other motor neuron disorders. A major emphasis of his research has been the initiation of clinical trials with innovative drugs in ALS. Prototyping and implementation of telemedicine and web-based solutions in home care management is a current goal of Professor Meyer in ALS.

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**SPEAKER: Professor Thomas Meyer**

**TITLE OF PRESENTATION: Comprehensive treatment in an interdisciplinary team**

**ABSTRACT:**

There are limited pharmacological options in ALS; the mainstay of management is symptomatic treatment. ALS patients who are managed at a multidisciplinary clinic may have a better prognosis than patients receiving a general medical care. A multidisciplinary team is essential for effective ALS treatment. Neurologists are responsible for the disclosure of diagnosis, prognosis and treatment options mainly of symptom management, and initiation of respiratory and nutritional interventions. Networking physicians including general practitioners, pulmonologists and palliative care specialists provide nutritional and respiratory support, pain management and palliative symptom control. Speech therapists monitor dysphagia and aspiration, and advice on compensatory swallowing techniques. Occupational therapists care for the optimization of the patient's environment including adaptive devices, and activity and home modification. Nutritionists monitor the nutritional status and the need for tube feeding and manage home enteral feeding. Physiotherapists perform physical therapy including exercises to promote strength, range of motion and endurance. There is a central role of the social worker counselling regarding employment, change in lifestyle and financial issues

The presentation focuses on nutrition management, respiratory support and communication in ALS. Non-invasive ventilatory support is standard of care for the treatment of hypoventilation and an effective therapy for symptom control and prolonged survival. When long-term survival is the goal, invasive ventilation may be offered. Full information of patients of burdens and benefits of long-term mechanical ventilation is required. In accordance with the principle of patient autonomy, physicians should respect the right of the patient for withdrawal of ventilation therapy and initiation of palliative care. Management of dysphagia, malnutrition and ALS cachexia includes modification of food and fluid consistency, postural advice, and enteral feeding. A percutaneous endoscopic gastrostomy (PEG) placement is indicated for those who have symptomatic dysphagia or significant weight loss. Patients and their families should be suitably counselled regarding the benefits and risks of the procedure. Appropriate alternative communication methods range from alphabet boards, to electronic speech output device including gaze communication systems using eye tracking to allow communication for those with very limited mobility.

All therapy options should be balanced against possibly iatrogenic difficulties, patient adherence, demands on carers, increasing dependence and unwanted prolongation of life. End-of-life decisions and the discussion of advance directives of these possibilities, respecting patient autonomy, have a major emphasis early in patient consultations.

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**SPEAKER:           Dr Brian Dickie**

**BIOGRAPHY:**

Brian Dickie graduated in 1991 with a Ph.D in Neuropharmacology from the University of Wales College of Medicine. He then took up a research fellowship in the Department of Pharmacology, University of Oxford, where his research on the mechanisms of cell death in Parkinson's disease was combined with teaching roles as Departmental Tutor and Lecturer in Neuroscience at Lincoln College, Oxford.

Since 1997, he has worked for the UK Motor Neurone Disease Association as Director of Research Development, with the job of providing strategic guidance, raising the Association's profile within the biomedical and care research communities, increasing the quantity and quality of Association-sponsored and collaborative research, organising the annual International Symposium on Amyotrophic Lateral Sclerosis/Motor Neuron Disease and communicating advances in MND research to lay and specialist audiences.

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**SPEAKER:           Dr Brian Dickie**

**TITLE OF PRESENTATION:           RESEARCH POLICIES IN ALS**

**ABSTRACT:**

In the past two years we have witnessed significant advances in identifying causes of causes of ALS. These discoveries are undoubtedly going to stimulate much more research around the world, improving our understanding of what causes motor neurons to die, generating new theories as to how we could stop this from happening and developing new and better ways of testing promising new therapies in the lab and the clinic.

How can funders of research, like DGM and the MND Association, best support the research community? There are some clear immediate aims: we need to find more causes of ALS; we need to generate new and more representative laboratory models; we need to improve the speed of diagnosis and measure disease progression more effectively; we need to attract the best young scientists and clinicians into ALS research.

We also need to work together more closely. ALS does not respect national boundaries, so the challenge for all of us is to ensure that the battle against this disease is not constrained by parochial policies and practices of researchers and the research funding bodies that support their vital work. The key to success lies in fostering strong international collaboration between key research teams, making biomedical resources and new technologies more readily available and sharing new understanding of the disease as rapidly as possible – all with the ultimate aim of finding effective treatments for this devastating condition.