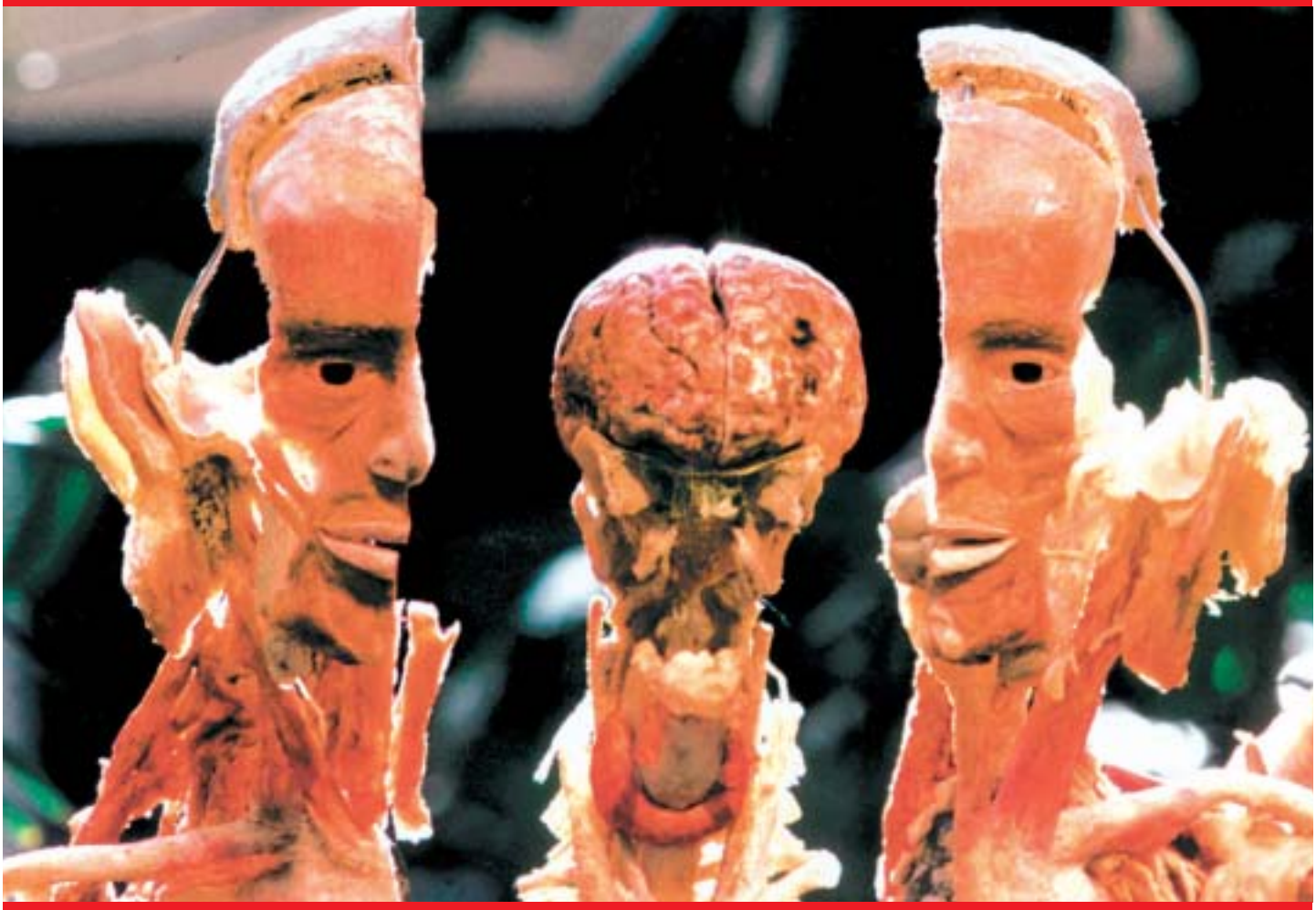
ISSN 1473-9348 Volume 2 Issue 5 November/December 2002

ACNR

Advances in Clinical Neuroscience & Rehabilitation



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Review Articles: Rehabilitation in Multiple Sclerosis; Patient organisations in the 21st century

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Date of Review: December 2001.

Date of Preparation: August 2002.

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Editorial Board and contributors

Roger Barker is co-editor in chief of Advances in Clinical Neuroscience & Rehabilitation (ACNR), and is Honorary Consultant in Neurology at The Cambridge Centre for Brain Repair. He trained in neurology at Cambridge and at the National Hospital in London. His main area of research is into neurodegenerative and movement disorders, in particular parkinson's and Huntington's disease. He is also the university lecturer in Neurology at Cambridge where he continues to develop his clinical research into these diseases along with his basic research into brain repair using neural transplants.

Alasdair Coles is co-editor of ACNR and contributes our Anatomy Primer. He is a Wellcome Advanced Fellow working on experimental immunological therapies in multiple sclerosis, based at the Dunn School of Pathology in Oxford and Department of Neurology in Cambridge.

Stephen Kirker is the editor of the Rehabilitation section of ACNR and Consultant in Rehabilitation Medicine in Addenbrooke's NHS Trust, Cambridge. He graduated from Trinity College, Dublin in 1985 and trained in neurology in Dublin, London and Edinburgh before moving to rehabilitation in Cambridge and Norwich. His main research has been into postural responses after stroke. His particular interests are in prosthetics, orthotics, gait training and neurorehabilitation.

David J Burn is the editor of our conference news section and Consultant and Senior Lecturer in Neurology at the Regional Neurosciences Centre, Newcastle upon Tyne. He qualified from Oxford University and Newcastle upon Tyne Medical School in 1985. His MD was in the functional imaging of parkinsonism. He runs Movement Disorders clinics in Newcastle upon Tyne and Sunderland. Research interests include progressive supranuclear palsy and dementia with Lewy bodies. He is also involved in several drugs studies for Parkinson's Disease.

Andrew Larner is the editor of our Book Review Section. He is a Consultant Neurologist at the Walton Centre for Neurology and Neurosurgery in Liverpool, with a particular interest in dementia and cognitive disorders. He is also an Honorary Apothecaries' Lecturer in the History of Medicine at the University of Liverpool.

Wojtek Rakowicz is a Specialist Registrar in Neurology. After training in Norwich and Cambridge he worked in the Neuromuscular Division at Washington University in St Louis. He is currently at the National Hospital for Neurology and Neurosurgery.

Simon Hickman trained at Cambridge University and Addenbrooke's Hospital. He did his general professional training in Nottingham and is now working as a clinical research fellow at the Institute of Neurology in London. His major interest is in optic nerve magnetic resonance imaging.

David Marsden award for young scientists - dystonia topics

The David Marsden Award will be presented for the first time in 2003 by the European Dystonia Federation. Professor David Marsden (1935 – 1998) was one of the leading neurologists in Europe and the Federation wishes to honour the enormous part he played in developing knowledge of and interest in dystonia.

The Award of 2,500 euros is intended to encourage research into dystonia in all European countries, especially by young scientists. Submissions are invited of papers (i.e. manuscripts for original publication – no abstracts) on either aetiology, pathogenesis, diagnosis and therapies on dystonia or the psycho-social effects on people with dystonia. Papers will be reviewed by the Federation's Medical Advisory Board.

Through the generous collaboration of the Movement Disorder Society (European Section) and the European Federation of Neurological Societies, the Award will be presented during the EFNS/MDS Congress -August/September 2003 in Helsinki. The winner will make a presentation of his/her findings at the Basal Ganglia Club meeting during the Congress, and at the Federation's own General Assembly in London - September 2003.

More detailed information and a submission form may be obtained at www.dystonia-europe.org or from the secretariat, 69 East King Street, Helensburgh, G84 7RE. Tel/Fax. 01436 678799, E-Mail. sec@dystonia-europe.org

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Date of preparation: August 2002.

Reference: 1. Cereghino J et al. Neurology 2000;55(2):236-242.

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contents

november/december 2002

Welcome to this new issue of the ACNR, and I apologise at the outset to the more basic scientific readers as this issue has more of a clinical slant than previous issues - but don't worry: the more basic scientific topics will appear. It remains to put basic research into some sort of clinical context. Indeed this need to bridge the gap between basic neuroscientific research and clinical neurology lay at the heart of the decision to develop this new journal, which is now nearly 2 years old, and remains its primary aim. This becomes an increasingly urgent mission. Unknown to many, the annual Neuroscience for Clinicians meeting in Cambridge, organised by Alastair Compston and sponsored by Brain, was cancelled this year because of a lack on interest. In the previous 11 years of its existence, there would always have been an oversubscription of young neurologists for the maximum 70 places on this superb course of lectures by eminent neuroscientists, including a handful of Nobel laureates. This year however, only 40 people were sufficiently interested in neuroscience to ask for a place on the course. This highlights the real danger that is facing clinical neuroscience, a discipline that is fast approaching extinction in the UK, under the relentless pressure to make doctors become service providers in the shortest possible training period. The importance of research as a part of all neurologists' training is becoming increasingly marginalised and regarded as a non-essential part of their education, which thus undermines those who do try to carry on with clinical research - especially those that try to take the laboratory to the clinic. This began with Calman training and has accelerated in recent years. UK clinical neuroscience is now on the critical list. So for those thinking about whether to go into research, then I plea that you carry on, because there is a real risk that in the UK such a person will become a collectors item!

Anyway, in this issue we have an example of how laboratory based research can inform clinical practice and vice versa. Jurg Kesselring, one of the modern pioneers of neurorehabilitation, discusses the relevance of rehabilitation to recovery in MS, highlighting the paucity of studies in this area. However, he does point out that plasticity is an integral part of the adult CNS and that this should be exploited. Indeed this is an area that could be massive in the future given the recent findings of the capabilities of adult neural precursor cells to repair ischaemic brain lesions (see Journal reviews), and the establishment by the MRC and other organisations to set up a UK stem cell bank (Meena & Rosser this issue).

We then have a new type of article from Russell & Jones about the growing role of patient organisations in the development of clinical services. This has proven critical in MS as well as a range of other conditions, for example the development of Parkinson's disease specialist nurses and the Huntington's and Motor Neuron Disease supportive services in the community. This is clearly an important topic and again is an area of development as the patients voice becomes more clearly heard, and the demands and services that the NHS can offer comes under closer scrutiny.

We also have a gem of a review article by Wojtek Rakowicz on inherited myopathies - an area that has changed dramatically in recent years as the gene defects underlying these conditions become increasingly recognised. We also have a cracking anatomy primer on the optic nerve and our usual clutch of journal reviews, conference reports and book reviews. Finally, we have an excellent article by Peter Misra on botulinum toxin in drooling - expanding the repertoire for this therapeutic agent, even though the use of it was first suggested about 180 years ago!!

So there we have it, another issue which we hope that you will find interesting and provocative, but if there are topics you would like to see covered then do let us know and we will see what we can do.

Roger Barker, co-editor

Features

Regulars

ACNR is published by Whitehouse Publishing,
7 Alderbank Terrace, Edinburgh EH11 1SX.
Tel. 0131 477 2335/07989 470278, **Fax.** 0131 313 1110
E-Mail. AdvancesinCNR@aol.com
Publisher: Rachael Hansford
Design & Production: Barbara Newton
Printed by: Stephens & George Magazines, Tel. 01685 388888.

Rehabilitation in Multiple Sclerosis

Authors

Professor Jürg Kesselring is Head of the Dept of Neurology at the Rehabilitation Centre in Valens. He is Chairman of the WHO Working Group on Multiple Sclerosis and of the International Medical and Scientific Board (IMSB) of Multiple Sclerosis International Federation (MSIF) and Vice-President of the Swiss MS Society. Professor Kesselring is also a Lecturer in Clinical Neuroscience at the Universities of Berne and Zürich.

Dr Serafin Beer was trained in neurology at the Kantonsspital St. Gallen and at the Neurological Department of the University of Berne, after his degree in Clinical Medicine at the University of Berne (Switzerland). He has been Consultant Neurologist at the Centre for Neurorehabilitation in Valens since 1995. Dr Beer is a member of the Medical Advisory Board of the Swiss MS Society.

Introduction

Multiple Sclerosis (MS) is a chronic inflammatory-demyelinating disease of the central nervous system leading to progressive impairment of various CNS systems. During the course of the disease a wide range of functional impairments and disabilities may develop which lead to psycho-social handicap and reduction of quality of life. New drugs such as beta-interferons and glatiramer acetate can modify the long term course of the disease by lowering relapse rate and slightly slowing progression of disability. Nevertheless the progressive course and early onset of MS with long survival time can have significant consequences on personal activities, social participation and quality of life. So for example, 15 years after disease onset 15% of MS patients need technical aids for walking and 29% use a wheelchair[1]. During the first 10 years after diagnosis 50–80% are out of work[2] and the socio-economic consequences of all this have only recently been addressed. The direct and indirect yearly costs amount to 90,000 Euros per patient per year, 17% of severely disabled MS patients requiring 50% of direct costs and 6.5% are living in institutions[3]. Health related quality of life in MS patients with moderate and severe disability is generally low, leading to a high level of depression[4].

The goal of rehabilitation is to reduce the consequences of the disease on function, personal activity, and social participation in order to allow the patients as much independence as possible with the highest possible quality of life. Evaluation of efficacy of rehabilitation in MS is particularly difficult: the disease course varies greatly beween and among individuals and is difficult to predict in different forms of the disease (relapsing-remitting, secondary progressive, primary chronic progressive). Triggers of relapses and progression are not well defined and the pathological processes (inflammation, demyelination, axonal loss, remyelination) may be heterogeneous and can not be discriminated accurately with standard neuro-radiological techniques[5], in particular, findings on MRI correlates poorly with the degree of disability. Therefore it is difficult to find a homogeneous patient group which satisfies scientific requirements for evaluating the efficacy of therapeutic interventions. This may explain the small number and methodological problems of studies published to date concerning the outcome of rehabilitation measures in Multiple Sclerosis. Earlier studies were mainly uncontrolled, and most were retrospective observations on small, heterogeneous patient groups[6-9]. More recently a few controlled trials have been published on this subject[5,10,11], only some of them, however, assess the impact on quality of life.

Comprehensive inpatient rehabilitation

Although treatment modalities vary in different rehabilitation centres, a consensus has been reached concerning the requirements and most important components of a rehabilitation programme[12,13]. Due to the broad spectrum of symptoms and disabilities, a comprehensive assessment of functional impairments and personal goals is essential in order to assemble an individually adapted, multidisciplinary, task and goal orientated therapy programme[14]. The therapeutic interventions themselves are only one part of the rehabilitation programme but of equal importance is the careful informative instruction of patients and their relatives in order to plan the needs after discharge. Management of specific symptoms and impairments such as spasticity and bladder dysfunction is also crucial in MS patients. Furthermore the use of medical and social resources may contribute to improving quality of life of patients and their relatives. Measuring outcome with adequate assessment systems is not only necessary from a scientific point of view but allows validation of efficacy of therapeutic modalities and adaptation or development of new therapies.

In an early prospective, uncontrolled study 20 chronic progressive MS patients not responding to outpatient therapy, achieved a significant improvement in various disability scores after an inpatient multidisciplinary rehabilitation programme of 53 days duration[6]. Another uncontrolled study showed a significant improvement using a short-term inpatient rehabilitation (15 days, N=79) programme on the different course patterns of MS, which lasted more than 3 months after discharge[8]. The benefit was more marked in patients with relapsing-remitting disease but significant improvements could also be documented in patients with progressive disease. These positive findings were confirmed in a later study[5] which was a prospective randomised, controlled study in which 32 patients underwent a 3 week inpatient multidisciplinary rehabilitation programme whilst the control group (N=34) were patients on a waiting list who were admitted for rehabilitation later. Patients were examined at the beginning of treatment and after 6 weeks. Patients in the control group showed a significant deterioration regarding disability and handicap, whereas the treated group showed significant improvement. Impairment measures, however, did not change.

The first study which included measurements of quality of life [Short Form 36 Health Survey Questionaire (SF-36) and Multiple Sclerosis Quality-of-Life questionaire (MS-QOL-54)] was a non-randomised longitudinal 1 year study, assessing the impact of an outpatient rehabilitation programme in a small patient group (n=12) with a waiting-list control population (n=19)[15]. The comprehensive treatment included daily physiotherapy, occupational and recreational therapy and information and help in coping with disabilities and social handicap. After 1 year significant improvement in physical health, pain, energy and fatigue, social support, cognitive ability, and general health were noticed in the treated group despite a decline in functional status. In a further prospective randomised, controlled study evaluating the impact of rehabilitation on quality of life, the effects of intensive inpatient physiotherapy (3 week duration, 2 x 45 min./day) in ambulatory MS patients (N=27) compared to a control group (N=23), which were instructed for a home programme[10], was assessed. After 3 and 9 weeks respectively a significant improvement of disability and mental quality of life as measured by the SF-36 was demonstrated, whereas there was no improvement on the physical composite score. After 12 weeks no significant difference could be noticed. On the functional level both groups were unchanged. An earlier similar study with lower duration and intensity of therapy could not find any significant improvement of mobility after inpatient physiotherapy[16]. In an MS group with chronic progressive disease (N=67), inpatient rehabilitation over 3 weeks led to a significant reduction of disability as compared to outpatient treatment[17]. This effect of therapy was demonstrated as well after 3 months, but after 12 months, no

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significant difference was demonstrated[18]. In a prospective, uncontrolled study, 50 MS patients with chronic progressive disease were investigated every 3 months after inpatient rehabilitation (23 days duration) and a significant reduction of disability and handicap was observed over 6 months[19]. In this study quality of life assessed by the SF-36 was improved in the physical score for 9 months and in the mental score for 12 months. These findings are particularly important because over the same period an increasing deterioration on functional level was observed demonstrating continuous progression of disease.

The comprehensive rehabilitation of MS patients with restoration of function seems not to be the main reason for improvement. Amelioration is mostly related to increased compensation, adaptation and reconditioning. Furthermore nonspecific effects (emotional coping, self estimation) are important. Information and instruction of patients and the use of medical and social resources may also contribute to improved coping with the disease and disability and therefore an improved quality of life of patients and their relatives. Thus, the specific effect of various therapy modalities is only one aspect of the long term effects observed in rehabilitation.

Specific therapy modalities

Fuller *et al.* were not able to demonstrate improvement on mobility after inpatient physiotherapy[16]. The same group examined the effect of outpatient physiotherapy in a prospective controlled cross-over study of 40 MS patients, randomised over 8 weeks, either in a specialised rehabilitation setting, at home or without any therapy at all. A significant improvement of mobility and reduction of disability could be demonstrated during therapy phases in comparison to phases without therapy. Furthermore the frequency of falls could be reduced. This effect was of short duration and could not be demonstrated after 8 weeks. No significant difference was shown concerning therapeutic effects of an outpatient treatment in the clinic and treatment at home[11].

A randomised controlled study (N=54) on the effect of aerobic training (3 times per week over 15 weeks) showed a significant improvement of aerobic capacity and of isometric strength compared to a control group[20]. Furthermore transient improvement of psycho-mental factors (anxiety, depression) and of fatigue could be observed in this study. More recently it has been demonstrated convincingly that a short term exercise training programme had positive effects on aerobic fitness, fatigue, health perception and activity level of subjects with multiple sclerosis[21].

Concluding remarks

According to criteria of evidence-based medicine none of the studies cited above will reach a Level-I-Evidence (large randomised study with high statistical power). However there is good clinical evidence for the efficacy of rehabilitation in MS[13]. An intensive inpatient multidisciplinary rehabilitation programme which is adapated for the individual, can reduce disability and handicap, thus allowing the patients better personal functioning and social participation. Together with better management of specific symptoms and disabilities, the quality of life of MS patients may be improved despite progression of disease. This improvement, especially concerning quality of life overlasts the specific treatment period for up to 6–9 months. Physiotherapy alone (inpatient or outpatient) as well as other specific therapy modalities may lead to improvement of mobility and reduction of disability but the effects are often relatively short-lived. The main reason for the long-term effect is most probably due to improved compensation, adaptation and reconditioning and better use of personal and social resources. Functional restoration seems to play a less important role as rehabilitation measures have no direct influence on the ongoing disease process and on the progression of the disease.

Several questions, however, remain. The optimal time, intensity, duration and specific components of therapeutic interventions in different MS patient groups are still to be determined. Concerning quality of life, controversies exist about whether generic assessment scales of health status are applicable in MS or whether more disease specific measures should be used.

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Correspondence to:

Prof Jürg Kesselring, Department of Neurology, Rehabilitation Centre, CH-7317 Valens, SWITZERLAND
Tel: ++41 3031408 Fax: ++41 3031410
E Mail: kesselring.klival@spin.ch

Patient Organisations in the 21st Century

Since the publication of *The NHS Plan* in July 2000, government rhetoric has consistently returned to the idea of the 'expert patient'. Patient influence, it was argued, is paramount to effective modernisation of the NHS, or, as chapter 10 put it, "care has to be shaped around the convenience and concerns of patients". This idea was elaborated, specifically in relation to the 17.5m people in the UK living with a long-term condition, in *The Expert Patient*, where the notion of patient and clinician sharing their particular "expertise" was explored[1].

The idea of the 'expert patient' was founded upon what has since become the most tired of buzzwords, 'empowerment'. This, it was argued, is to be fostered primarily through the provision of information and support. In the terms of the *Plan*, however, this is not understood as improving patients' knowledge of their disease, despite gestures towards making people more active in their own treatment. Instead the focus is on the need to understand the NHS and the way it works. In place of the Community Health Councils, the Blair government offers up a phalanx of new organisations, ideally with cute acronyms, to make the NHS intelligible and responsive. By the time a discussion document was produced in September 2001[2], no less than six new services and umbrella groups were being readied to enter the fray[3]. Discovering what has actually come into being, though, and indeed what ever will, is as hard as figuring out who you might actually want to approach for help.

Government plans, both consciously and unconsciously, have therefore increased immensely the role that patient organisations (POs) have to play in health service provision. Some traditional areas of PO activity, even if they are not supported directly, have been validated by the proposals, particularly disease and treatment related information – equal patient-clinician relationships, after all, will never be founded solely upon patient experience. New services like NHS Direct offer welcome support, but given their necessary breadth, their ability to provide in-depth support is limited.

Outside Parliament in April 2001. The picture shows (L-R) Bernadette Porter (MS specialist nurse, National Hospital for Neurology & Neurosurgery), Paul Burstow MP, Christine, and Sue Thomas, Royal College of Nursing, at the launch of the document Key Elements for developing the MS specialist nurse services in the UK.

POs, on the other hand, are usually focused on one specific disease or condition, and have thus become the major source of clear, usable information resources for patients and their families. The MS Trust produces booklets, for example, to explain simply what a diagnosis of multiple sclerosis means, both in pathological and symptomatic terms; or to explain to a child what is happening to a parent with MS. Such booklets are complemented with phone information services, internet resources, and communication through E-Mail, letters or face-to-face.

With the plans for increasing patient and public involvement in the NHS, meanwhile, still very much at a 'transition' stage[4], POs have also been required to provide more information for patients trying to find their way round the cloudy maze that is the NHS. The risk-sharing scheme for disease modifying drugs for MS provides a good example, as a very high profile development in NHS policy led to high levels of public confusion. The MS Trust continues to respond to numerous queries about the potential benefits or side-effects of the drugs, the differences between the various brands, who qualifies for the scheme, who to see to be selected, and which centres are currently prescribing. Until the new government bodies are functional, and possibly long afterwards, POs will continue to provide the guidance that people need as they come to grips with the NHS, helping to create the informed, 'empowered' patient body that is so central to the government's idea of effective reform.

Elsewhere, however, POs have increasingly been brought into the process of service provision itself. Many POs operate services that are complementary to standard NHS systems – for instance the Motor Neurone Disease Association's team of regional care advisers. But other POs' work is beginning to cover areas that have traditionally been the preserve of statutory services. The concept of 'self-management' that was so central to *The Expert Patient*, for instance, is ultimately dependent on their involvement. The political mileage obtained from this idea was only made possible by the successes of programmes run by organisations such as Arthritis Care and the MS Society – highlighted by the report as exemplary responses to the peculiar demands of chronic illness. Previous administrations were perhaps afraid of the loss of control potentially involved in partnership programmes, but while 'private finance initiative' projects may still possess a controversial aspect, the current government does appreciate the utility of sharing costs with charities. The MS Society's 'Nurse Fund' for MS specialist posts is a noteworthy example of the successes that an injection of voluntary income can provide.

Such steps are reinforced by the commitment POs have given to improving the knowledge of health professionals about particular diseases and their treatment. The NHS has always lacked the resources for training its staff in such a focused manner, and so POs have increasingly taken on a wider and wider educational remit. All new MS specialist nurses, for instance, are given training in the management of MS by the MS Trust, through intensive induction courses and regular follow-ups. Further educational programmes have been aimed at a broader audience of health professionals, frequently with the purpose of facilitating effective multi-disciplinary team interaction.

These developments have been driven both by the need to improve the support that patients receive, and by the lack of government resources available to meet this need. This second factor has of course also been crucial in making evidence based practice a necessity for strategic medical planning. Driven by the need for efficiency, decisions must now as far as possible be taken on the basis of systematic reviews of RCTs. And yet the government and DoH do not generally have the funds for such research. The role of the MS specialist nurses, for instance, was defined by a piece of research funded by the MS Trust[5], research which has since enabled the Trust to refine the training that such nurses receive.

In light of the recent 'cross cutting' Treasury review[6], and the allocation of over £200m for its implementation and the creation

Authors

Jonathan Russell has worked at the MS Trust since graduating from Jesus College, Oxford earlier this year. Christine Jones is chief executive of the MS Trust and has worked in the voluntary sector for over twenty years. The MS Trust has been actively involved with NICE drug appraisals and guideline development, as well as the DoH risk-sharing scheme, processes in which the need for close partnership between professional and patient organisations has become ever more apparent.

of the '*future*builders' investment fund, it seems that these developments in the level of PO involvement in the NHS will continue to grow. Despite this extra cash, however, the potential dangers for organisations that directly depend on the good will of their supporters must also be kept in sight. For POs have not only had to commit massive amounts of time, energy and money to information, research, education and other services; they have also had to put their name behind projects whose direction they cannot necessarily control. This is nowhere more apparent than in their participation in service design. The government needs PO input in this seemingly endless consultation process to fulfil their intention of representing the patient's voice in the reformation of the NHS. The paradoxes of such an aim are clear, however, when it is realised that National Service Frameworks and NICE guidelines are themselves intended to create clearer national standards "so that patients can see what to expect from high quality services". POs are there to represent the needs of their supporter groups, but unavoidably become part of a system that can only work through compromise, and which is ultimately aimed at telling patients what they can expect. This is rational enough, but in one step POs have been separated from the basic source of their strength, and the very idea of patient-driven reform seriously debased.

This situation is perhaps a suitable emblem for the difficulties facing POs as they enter the 21st century. They face the most testing of tight-rope walks, balancing between government and public, pushing for achievable changes while maintaining the integrity of their guiding principles. The possibility of the NHS being effectively reformed depends to a large degree on their active participation; but if they become too closely associated with projects that are perceived by the public as fundamentally flawed, they risk losing the support on which their own existence depends. The risk-sharing scheme is a most apposite example. The agreement offers the potential for great benefits for a large number of people with MS, but the difficulties involved in its implementation, and the compromises already made to allow it to reach this stage, are increasingly apparent. The MS Trust's involvement in the selection of the group that will run the scheme, and the monitoring of its progress, has meant not just a huge commitment of resources but also an association that might prove highly damaging should the scheme not take off – even though many aspects of its implementation lie in the hands of the DoH and the SHAs. In this respect the co-operation of different POs and relevant professional bodies such as the ABN continues to be vital. Neurology remains a particularly under-funded and under-manned area of the NHS, but together such organisations are much more powerful in improving services, indeed too powerful to be ignored. Governmental pragmatism will always prove a stumbling block for patient expectations, but if professional and PO voices and efforts are directed to similar and consistent ends a health service that directly serves the needs of its patients remains wholly achievable.

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Correspondence to:

Jonathan Russell, Multiple Sclerosis Trust, Spirella Building, Letchworth, SG6 4ET. Tel. 01462 476707, www.mstrust.org.uk

Botulinum toxin as a treatment for drooling of saliva

Author

Dr. V. Peter Misra MD FRCP is a Consultant in Clinical Neurophysiology at the National Hospital for Neurology & Neurosurgery, Queen Square, London where he runs an EMG guided botulinum toxin clinic.

Drooling of saliva, as a consequence of difficulty with swallowing either because of pharyngeal muscle weakness, reduced spontaneous swallowing or incordination, is a common and disabling condition which contributes to a poor quality of life and to carer burden. It can be seen in association with a wide number of neurological disorders (Table 1).

The parotid, sub-mandibular and sublingual salivary glands account for about 90% of daily salivary production while the lingual and other minor salivary glands secrete about 10%. Normal daily salivary production is 1 to 1.5 litres. The salivary glands are controlled by the autonomic nervous system, mediated by adrenergic and cholinergic nerve endings, and are primarily under parasympathetic control.

In 1822, Justinus Kerner, a German poet and physician, noting the severe dryness of mouth in patients with botulism first suggested that the toxic substance causing botulism might be useful in treating hypersalivation[1]. But it has only been in the last few years that Botulinum toxin Type A (BTXA) has been used for this purpose[2-8]. BTXA binds selectively to cholinergic nerve terminals and rapidly attaches to acceptor molecules at the pre-synaptic nerve surface. Internalised BTX inhibits the release of acetylcholine from the synaptic vesicles into the synaptic cleft resulting in reduced function of parasympathetic controlled exocrine glands (or reduced muscle contraction in the case of neuromuscular junction). The blockade though irreversible is temporary as new nerve terminals sprout to create new neural connections.

Table 1: Common neurological disorders associated with drooling of saliva
- Parkinson's disease and other akinetic rigid syndromes
- Motor neurone disease with involvement of bulbar muscles
- Cerebral palsy
- Post stroke
- Post-traumatic encephalopathy

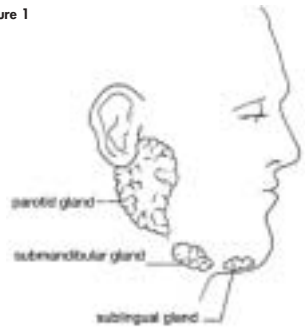
BTXA as a form of treatment for salivary drooling has proved attractive especially as, on the whole, other treatments available for sialorrhoea are often unsatisfactory. Systemic anticholinergic drugs are often ineffective and produce side effects such as blurred vision, urinary retention and cardiac arrhythmia especially in the elderly[9]. Surgical intervention[10] and local irradiation of salivary glands[11] may also be considered but these are invasive and relatively major procedures.

Table 2: Methods of assessing salivary production and drooling:
- 1-10 visual analogue scale (where 1 is best possible improvement and 10 is the worst possible situation)based on the patient/carer observations
- Counting the number of standard sized paper handkerchiefs used in the course of the day
- Inserting gauze rolls of known weight into the mouth for a short period of time and calculating the difference between the wet and dry weight of the gauze rolls.
- Salivary gland scintigraphy

Drooling of saliva can be affected by impaired alertness and cognitive decline, stooped posture and by the degree of bulbar dysfunction; it can also tend to be episodic. With all of these fluctuating variables a quantitative assessment of the efficacy of BTXA treatment on the amount of salivary production and of drooling often proves to be difficult. Table 2 lists the methods by which such assessments have been made; none of these are perfect and may often need to be used in combination. In most studies the benefits of treatment have overall been reported as being reasonably good. However the variables and episodic nature of the problem coupled with fluctuations based on impaired alertness and cognitive dysfunction, reduced physical activity and posture makes accurate assessments difficult.

In the relatively few reports that appear in the literature, injections of BTXA have been made percutaneously into the parotid and in some cases both the parotid and submandibular glands. In almost all reports in the literature the injections have been made blind but in one report the injections were made under ultrasound control to avoid vascular structures and the branches of the facial nerve.[7]

Figure 1



"In 1822, Justinus Kerner, a German poet and physician, noting the severe dryness of mouth in patients with botulism first suggested that the toxic substance causing botulism might be useful in treating hypersalivation."

The reported doses of BTXA used vary between 5-40 mu of Botox (Allergan) for each parotid gland and 2.5-15mu of Botox (Allergan) for each submandibular gland. If Dysport (Ipsen) is used the equivalent doses will need to be used. There is an unresolved debate as to the appropriate equivalent dosage between the two products. It has been reported to vary between 1:3 and 1:6, the wide differences are probably because of methodological reasons. The three larger randomised controlled studies that have tried to answer the question have reported bioequivalence ratios of Botox to Dysport of 1:4[12] ,1:3 or below[13,14]. Trials in patients with cervical dystonia treated with botulinum toxin type B (BTXB) have reported an increased incidence of dryness of the mouth[15], this may suggest that a smaller dose of BTXB could cause the same effects with reduction in the potential for dysphagia. Trials using BTXB are planned.

The main side effect of this form of treatment is dysphagia,

Table 3: Potential side effects of BTX treatment for salivary drooling.
- Dysphagia
- Weak mastication
- Damage to the facial nerve/artery
- Dental caries
- Parotid gland infection

due to diffusion into nearby bulbar muscles. Mastication can also be weakened due to unwanted weakness of the masseter muscles. These effects would appear to be related to injection placements and dose. EMG guided injection can prevent inadvertent injection into the masseter muscle and improved delivery of BTXA by injecting retrogradely through Stenson's duct is being investigated and may prove to be a useful procedure. Other potential side effects are listed in Table 3.

In order to prevent the potentially serious side effect of dysphagia it is prudent to initially begin treatment with only between 6 to 14 mu of Botox (Allergan) to each parotid gland (divided into 2 sites) depending on the amount of drooling (Figure 1).

If with this dose the clinical response is felt to be insufficient the procedure may be repeated after 2 weeks. If still ineffective the submandibular glands may then be injected with 5mu of Botox to each gland. The effect of the BTXA is temporary and lasts for between 3-6 months and hence repeat injections are necessary.

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The Effective Management of Headache

Edited by: Peter J Goadsby, Andrew J Dowson, Andrew Miles
Publisher: Aesculapius Medical Press, 1999
Pages: 164
ISBN No: 1-903044-03-0
Price: £19.99

Whether or not one believes headache to be a symptom best dealt with by neurologists, or even a neurological illness, virtually every neurologist in the country sees, willy-nilly, many complaining of this problem, and hence strives to achieve the effective management of headache. To what extent can this slim volume, one of a series of titles published as "UK Key Advances in Clinical Practice Series 2000," assist in the fulfilment of this goal?

The text is divided into two sections: "Evidence and Assessment," and "Evidence and Treatment." From the perspective of this reviewer, the latter is the more rewarding reading, if, that is, one is wishing to learn about migraine, rather than headache per se. There are chapters dealing with prophylaxis, the relative merits of the triptans (prior to the licensing of almotriptan), migraine in women and children; but there is little on the more prevalent problem of tension-type headaches. Indeed, the longest entries in the index for tension-type headache relate to acupuncture and spinal manipulation, parts of a chapter devoted to complementary therapies. For those who believe that prescribing pills may not be the most appropriate response to this clinical problem, this carefully argued chapter makes particularly interesting reading.

Less satisfying is the "Evidence and Assessment" section. Chapter titles which particularly caught my eye, such as "When to refer: a primary care perspective" and "Psychiatric perspectives on headache," failed to deliver. The former argues that much can be achieved within the primary health care team prior to referral, using a step by step approach to treatment. Undoubtedly true, but seldom coinciding with my experience, most patients being referred to my clinic after a single GP consultation and after trying only a single analgesic. Moreover, the indication for referral advocated here seems to be intuition. The latter chapter is clear that psychological factors are important in the aetiology and maintenance of headache in some patients, but left me with no clear idea of how frequently, or of how to identify and manage them (referral to a psychiatrist, or a pain psychologist?).

Maybe I began this book with inappropriate expectations, perhaps due to the title. I would have liked an airing of the thorny debate on the place, if any, of CT scanning in patients with tension-type headache. Some consultants condemn such a practice as almost sinful, because of the extremely remote possibility of finding pathology, and because of the risk of reinforcing patients' erroneous belief in serious underlying pathology (most patients in my experience seem to expect this, and want a scan); whereas others routinely perform scans in the hope of allaying patient fears, however unlikely pathology seems on clinical grounds, and to achieve closure of the patient episode. Is it known whether patients fare better, or reattend less, if scanned?

For those interested in this book, ask your librarian: apparently every hospital library in the UK has been provided with a copy, courtesy of the Migraine Trust.

AJ Larner, WCNN, Liverpool

Essential Neurology

Edited by: I.M.S. Wilkinson, 3rd Edition
Publisher: Blackwell Science.
Pages: 248 pp
Price: £20.95

I bought this book to use in the preparation for my Final Medical examinations and found it to be extremely useful. Unlike other Neurology textbooks offering only key information, Essential Neurology lays out core information in a user-friendly manner which is always accompanied by key details and points of discussion. This allowed me to firmly grasp important information of which I previously had little understanding, without spending hours toiling through the irrelevant detail encountered in voluminous Neurology textbooks.

The book divides the subject of Neurology into 13 chapters of approximately equal size, which correlate with the 13 key areas in Neurology. Each chapter is further divided into conditions occurring under that category. The information is systematically presented, allowing a clear mental picture of the role of the particular conditions discussed in the vast framework of neurology. Each condition is subdivided once again into causes, clinical features, treatment and prognosis, with particular emphasis on the clinical picture and a holistic approach to care. This allows the reader to understand the clinical manifestations very clearly, and appreciate that treatment consists of focusing on all areas affected. Important areas of Neurology such as Paraplegia and Epilepsy are reserved their own chapters and the book's systematic approach is illustrated in its stepwise discussion of Nerve Root, Nerve plexus and Peripheral nerve lesions in the chapter of the same name.

The art of neurology lies very much in the correct assembly of symptom and sign 'parts' to form the architecture of the diagnosis. In my view the book would become even more appealing if each chapter contained a sample case history relating to its content, showing how the clinical features are used to formulate the diagnosis. Another feature that would have made Essential Neurology invaluable during my pre-exam days is a brief summary box at the end of each chapter reiterating the crucial fundamental concepts that one could simply glance over.

The style of the author is precise and crisp with bullet points used to convey key factual details and explanations offered in full prose. All neurological concepts are beautifully discussed. A diagrammatic approach parallels a written explanation of each concept, and the book's margins are filled with pictorial representations and aides de memoirs closely following the text. This not only makes the read more interesting and appealing, but it also allows constant consolidation of the knowledge gained from the text.

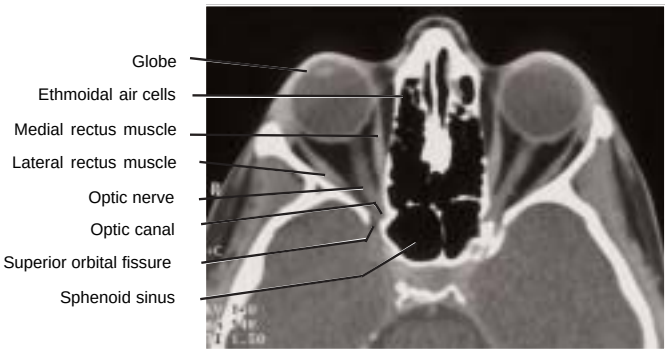
Mithu Mukherjee, Cambridge

Optic nerve

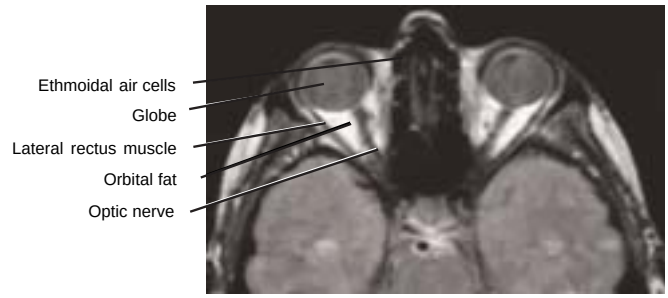
The Basics. The optic nerve runs from the optic nerve head at the back of the eye to the optic chiasm. It contains about one million axons from the ganglion cells of the retina, half of which cross over in the chiasm, to proceed as the optic tract to synapse in the lateral geniculate body, pulvinar, and superior colliculus.

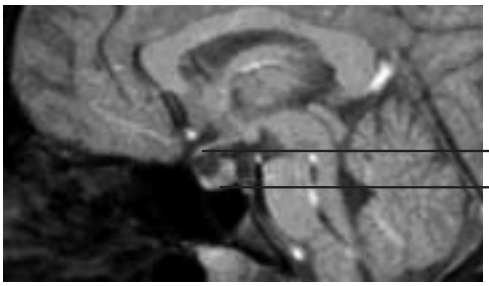
The optic nerve develops as an offshoot of the brain and is covered by a sheath, made up of the full three layers of meninges in continuity with the leptomeninges of the brain, which transmits the cerebrospinal fluid (CSF). Raised intracranial pressure is therefore communicated through to the optic nerve head and is visible as papilloedema on fundoscopy. Its blood supply comes from the ophthalmic artery, a branch of the internal carotid artery. As in the rest of the central nervous system, its nerve fibres are myelinated by oligodendrocytes rather than Schwann cells, which myelinate peripheral nerves. The optic nerve is therefore the only cranial nerve vulnerable to inflammatory demyelination in multiple sclerosis.

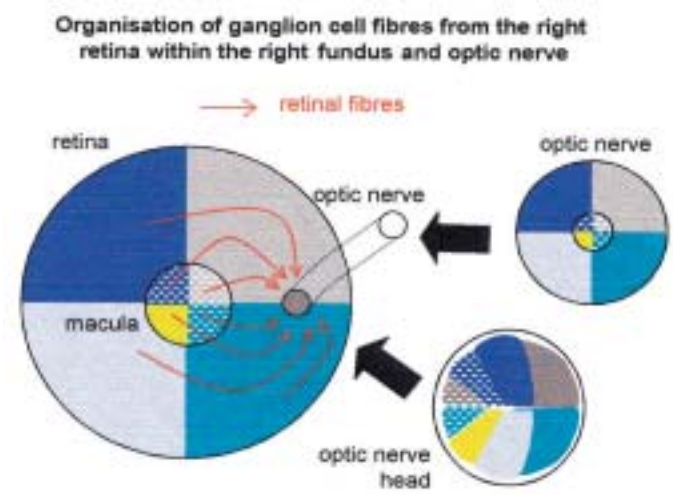
CT scan of the optic nerves



MRI scan of the optic nerves







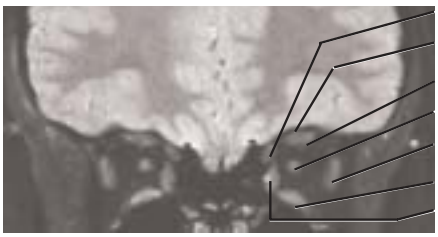
Organisation of nerve fibres within the optic nerve

Nerve fibres from the macula project directly to the temporal side of the optic nerve head, with peripheral retinal input converging more indirectly from the nasal side. Hence atrophy of the macular fibre bundles leads to temporal pallor of the disk. Within the first few millimetres of the optic nerve itself, the fibres are rearranged to form a retinotopic distribution.

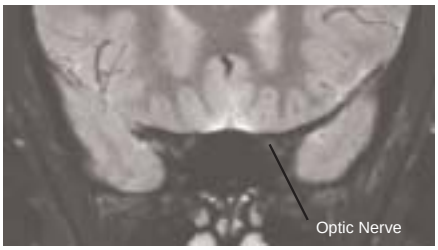
The macular fibre bundle is vulnerable to demyelination, toxins and metabolic deficiency leading to a central scotoma. Branch occlusions of the retinal artery however cause field defects which respect the meridian. Lesions of part of the macular bundle, such as occur in glaucoma, cause arcuate scotomata.

Within the optic nerve, the macular fibres are most vulnerable to pressure. Hence compression of the optic nerve anywhere along its course usually first causes a central scotoma.

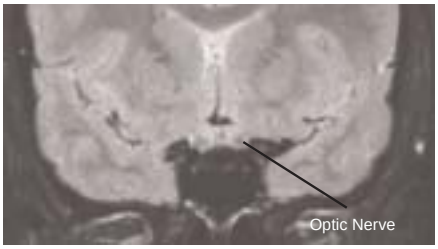
Simon J. Hickman and Alasdair Coles



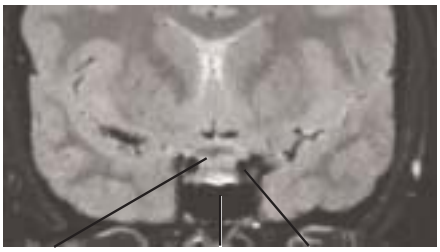
Optic Canal



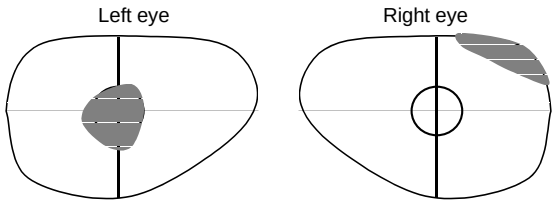
Intracranial portion of the optic nerve



Optic Chiasm



Central and "Junctional" Scotoma



Divisions of the optic nerve.

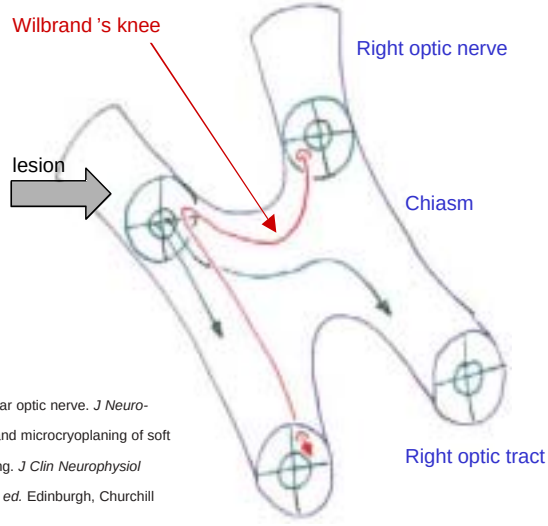
The optic nerve is about 40-50mm long and is subdivided into four parts.

The **intraocular portion** of the optic nerve measures 1.8 mm by 1.5 mm in diameter and 1 mm in length. The ganglion cell axons turn posteriorly to exit the globe perpendicular to the surface layer. They are divided into bundles by Müller cells in the retina and continue as bundles separated by fibrous septa.

The **orbital portion of the optic nerve** is 20-30 mm long and has about 6mm of slack to accommodate orbital movements. It is contained within an outer sheath of dura mater and an inner sheath from the arachnoid. The surrounding orbital fat contains the ciliary vessels and nerves. 6-12 mm from the globe, the central artery of the retina perforates the optic nerve with its accompanying vein, and runs within it to the retina. As the nerve enters the **orbital** (or "optic") **foramen** its dural sheath becomes continuous with that lining the orbit and the optic foramen. The **optic canal** is formed by the union of the two roots of the lesser wings of the sphenoid bone. The limited space within the canal and its bony walls makes the nerve vulnerable to damage here from blunt trauma. In the optic canal the ophthalmic artery lies below and to its lateral side.

The **intracranial portion of the optic nerve** is about 10 mm long and culminates in the optic chiasm. Compressive lesions here usually first give a central scotoma and then a "junctional scotoma". Traditionally this latter is ascribed to involvement of "Wilbrand's knee": lower nasal fibres from the unaffected nerve, which sweep forward as they cross over at the chiasm. However, these fibres were demonstrated in patients who had had enucleations and therfore may be artefactual. Junctional scotomas could arise through chiasmal involvement.

Lesion of the intracranial portion of the left optic nerve



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Inherited Myopathies

Dystrophic and non-dystrophic inherited muscle diseases have traditionally been defined by the presence or absence of prominent muscle fibre degeneration on biopsy. Huge advances in our molecular genetic understanding of the inherited myopathies have made this nosological distinction less clear[1-3] but the recognition of characteristic phenotypes is still an important part of the diagnosis.

Author

Dr Wojtek Rakowicz is a Specialist Registrar in Neurology. After training in Norwich and Cambridge he worked in the Neuromuscular Division at Washington University in St Louis. He is currently at the National Hospital for Neurology and Neurosurgery.

Presentations of inherited myopathies

Inherited myopathies commonly present with weakness, contractures or cardiac dysfunction, frequently only in adulthood. In the absence of a family member with a confirmed diagnosis, individuals are investigated with measurement of the serum creatine kinase level (typically extremely high), EMG, (immuno)histochemical analysis of a muscle biopsy specimen, ECG and echocardiography. Genetic testing may also be required.

PATTERNS OF WEAKNESS

The early involvement of selective muscle groups is a prominent feature of the inherited myopathies. **Limb-girdle** (shoulder and pelvic girdles) weakness, a non-specific finding in muscle disease, is more likely to be due to an inherited myopathy if associated with toe-walking (Table 1). The weakness in **distal myopathies** (Table 2) typically affects muscles in the forearm and lower leg more than the intrinsic muscles of the feet and hands, distinguishing it from neurogenic processes. Early selective **facial** weakness, **ocular and bulbar, periscapular** and **humeroperoneal** (e.g. biceps and tibialis anterior) weakness are strongly suggestive of inherited myopathies (Table 3). Prominent **asymmetry** is a distinctive and necessary feature of facioscapulohumeral dystrophy.

CONTRACTURES

Contractures, caused by tendon shortening and restrictive changes in the joint capsule, can occur in any immobile joint but are particularly common in inherited myopathies. The result is a fixed reduction in the range of joint movement that feels more like bone than a tight tendon, for instance at the ankle, knee, hip or elbow. Ankle contractures due to shortening of the Achilles' tendon give rise to the toe-walking so characteristic of boys with Duchenne's muscular dystrophy. It is rare for contractures to be prominent early in the course of neuromuscular disease but they are a presenting feature of Emery-Dreifuss muscular dystrophy and Bethlem myopathy at a time when muscle weakness is minimal or absent.

CARDIAC INVOLVEMENT

Many of the inherited myopathies are associated with cardiac dysfunction which must be sought with ECG and echocardiography and may require the insertion of a pacemaker. Cardiomyopathy in the dystrophinopathies may present with tachycardia at rest. Cardiac conduction defects are frequently seen in myotonic dystrophy and may be followed by the development of a cardiomyopathy. Individuals with Emery-Dreifuss muscular dystrophy are particularly prone to bradycardia that may present with syncope or sudden death.

Inherited myopathies presenting with limb-girdle weakness

DUCHENNE'S (DMD) & BECKER'S (BMD) MUSCULAR DYSTROPHIES

DMD and BMD are allelic variants in which mutations of the dystrophin gene give rise respectively to absent or reduced protein expression. Mutations generating a premature stop codon abolish dystrophin expression and result in the more severe DMD phenotype. Residual expression of dystrophin, typically a truncated protein, gives rise to BMD which can be very mild indeed, including individuals with cramps and post-exercise myalgia or myoglobuinuria. Cardiac involvement is frequent in DMD and BMD and can even affect carriers of the mutation; the severity of the cardiomyopathy bears no relation to the degree of limb weakness.

Due to the size of the dystrophin protein, three antibodies (directed against the -NH_2/-COOH terminals or the rod domain) are used to demonstrate the immunohistochemical absence of

TABLE 1: Inherited myopathies presenting with proximal weakness
Inset: Massive calf hypertrophy in DMD

PROXIMAL INHERITED MYOPATHIES	CHARACTERISTIC MUSCLE INVOLVEMENT	INHERITANCE *age at onset*	MOLECULAR DIAGNOSIS
DMD Duchenne's muscular dystrophy	toe-walking calf hypertrophy Gower's manoeuvre cardiomyopathy	X-linked *3-5y*	mutations in dystrophin gene • absent staining • DNA studies
BMD Becker's muscular dystrophy	as for DMD but much milder post-exercise cramps cardiomyopathy	X-linked *3-20+y*	mutations in dystrophin gene • normal/reduced staining • DNA studies
LGMD Limb-girdle muscular dystrophies	pelvic>>shoulder girdle can look like DMD, BMD or humeroperoneal weakness sparing face no cardiac involvement	AR (AD) *3-20+y*	various mutations incl. calpain-3, / -,€,ℑ, ℘sarcoglycans • absent/reduced staining • Western blotting
PROMM Proximal myotonic myopathy (DM2)	limb-girdle stiffness, pain myotonia cardiac conduction defects can be similar to DM1	AD *20-60y*	quadruplet expansions in ZNF9 • DNA studies

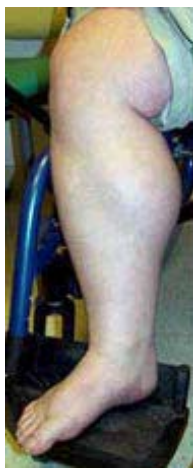
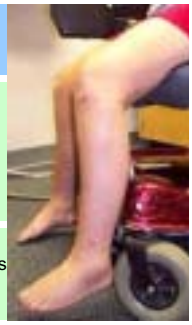


TABLE 2: Inherited myopathies presenting with distal weakness
Inset: Early selective posterior compartment weakness and wasting in LGMD2B

DISTAL INHERITED MYOPATHIES	CHARACTERISTIC MUSCLE INVOLVEMENT	INHERITANCE *age at onset*	MOLECULAR DIAGNOSIS
Myotonic dystrophy	myotonia bilateral ptosis masseter/temporalis sternocleidomastoid bulbar muscles cardiomyopathy	AD *any age*	triplet expansions in DM-PK • DNA studies
Distal myopathies • Welander • Nonaka • Miyoshi/LGMD 2B	no cardiac involvement • forearm extensors • anterior compartment leg • posterior compartment leg	 AD *>40y* AR *<30y* AR *<30y*	few identified genes • myopathic biopsy ± inclusion bodies • Miyoshi/LGMD2B allelic disorders with decreased/absent dysferlin



the full-length molecule in DMD. Staining may be normal or only minimally reduced in BMD. A detectable deletion or duplication in the dystrophin gene is found in 70% of DMD, the remainder being due to point mutations or small rearrangements that cannot be routinely screened in such a large gene. Treatment with oral or pulsed intravenous steroids is routine in the US[4] but not in the UK. With more attention to multidisciplinary, and especially respiratory, care many boys with DMD are living well into their third decade.

LIMB-GIRDLE MUSCULAR DYSTROPHY (LGMD) SYNDROMES

The LGMDs are a large group of inherited disorders with a range of presentations including phenotypes indistinguishable from DMD or BMD as well as non-specific limb-girdle weakness. In an undiagnosed early-onset myopathy disproportionate pelvic girdle weakness is suggestive of a LGMD where proximal lower limb weakness often predates shoulder girdle weakness even by many years (e.g. calpainopathies, LGMD2A). The dysferlinopathies (LGMD2B) differ from other LGMD syndromes with a later (adolescent) onset and striking distal weakness, particularly in the gastrocnemii (cf. distal myopathies).

Most LGMDs have an autosomal recessive pattern of inheritance. They are frequently associated with deficiencies in dystrophin-associated proteins, especially the sarcoglycans (LGMD2C-F). Diagnosis currently depends on demonstrating absent or reduced protein expression on muscle immunohistochemistry or Western blotting. It is recognised, however, that a reduction in protein expression is not always the primary molecular defect but may be secondary to another pathogenic process.

PROXIMAL MYOTONIC MYOPATHY (PROMM)

PROMM (or DM2) is an autosomal dominant disorder that gives rise to muscle weakness, stiffness or pain in a limb-girdle distribution and cataracts. The distribution of weakness, frequent calf hypertrophy, normal face and absence of central nervous system involvement distinguish PROMM from myotonic dystrophy (DM1). This distinction, however, is not absolute and distal weakness similar to DM1 can also be seen. PROMM is caused by an expansion in the number of $[CCTG]_n$ repeats in the gene encoding zinc finger protein 9 (ZNF9). While there is some intergenerational instability in the size of the repeat, anticipation is not a prominent clinical feature.

Inherited myopathies presenting with distal limb weakness

MYOTONIC DYSTROPHY

The clinical features of myotonic dystrophy (DM1) are among the most characteristic of any neurological disease and include extramuscular manifestations such as frontal balding, cataracts and diabetes. Myotonia, best sought in the thenar eminence and wrist extensors, is accompanied by strikingly distal limb weakness affecting particularly the foot extensors and the forearms but initially sparing the intrinsic muscles of the foot and hand.

Molecular genetic confirmation of the diagnosis of myotonic dystrophy is made by the demonstration of an expansion in the number of $[CTG]_n$ triplet repeats in a non-coding region of the dystrophia myotonica protein kinase (DM-PK) gene. The phenomenon of genetic anticipation (earlier symptom onset in successive generations) is the result of an intergenerational increase in the number of repeats.

DISTAL MYOPATHIES

The distal myopathies can be divided into autosomal dominant disorders with late (>40 years old) onset (e.g. Welander-type) and autosomal recessive disorders with earlier (<30 years old) onset (e.g. Miyoshi- and Nonaka- type). The biopsy is myopathic rather than dystrophic and frequently contains inclusion bodies reminiscent of those seen in (sporadic) inclusion body myositis and hereditary inclusion body myopathies.

Welander distal myopathy is unusual in that weakness starts in the arms (especially wrist and finger extensors) rather than the legs and, in contrast to other distal myopathies, wasting of the intrinsic muscles of the hand occurs early. Nonaka distal myopathy (also known as hereditary inclusion body myopathy type 2) starts in the legs with preferential involvement of muscles in the anterior compartment. Miyoshi-type distal myopathy is allelic with LGMD2B (dysferlinopathy) with which it shares distal leg onset in the posterior compartment (i.e. wasted as opposed to hypertrophied gastrocnemii).

Distinctive inherited myopathy phenotypes

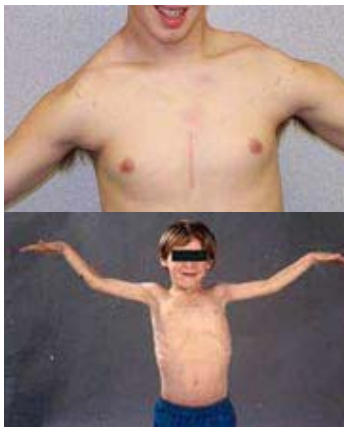
FACIOSCAPULOHUMERAL (FSH) MUSCULAR DYSTROPHY

FSH is a relatively benign asymmetric myopathy with no cardiac involvement, a normal life expectancy and only 20% lifetime risk of being wheelchair-bound. Although symptom onset is most typically during adolescence, individuals with FSH frequently present to adult neurology clinics with sporadic (10% of mutations are new) asymmetric muscle weakness: the absence of asymmetry makes the diagnosis unlikely. Facial weakness is invariably found on examination but may be very mild and shoulder girdle symptoms, including pain, are more likely to trigger presentation. Impaired shoulder abduction with elevation of the shoulder blades ('triangular shoulders') is the result of reduced scapular fixation and not weakness of the deltoids which are characteristically spared. Scapular winging is frequently observed but not invariable.

Limb weakness is in a humeroperoneal distribution and can result in a symptomatic footdrop. FSH is diagnosed by the demonstration of a chromosomal deletion, a reduced number of 3.3kb repeats at 4q35 but no single gene defect has been identified.

TABLE 3: Inherited myopathies presenting with distinctive patterns of weakness
Top inset: Impaired scapula fixation ('Triangular neck'), relatively spared deltoids in FSH; Bottom inset: Elbow and wrist contractures in EDMD.

DISTINCTIVE INHERITED MYOPATHIES	CHARACTERISTIC MUSCLE INVOLVEMENT	INHERITANCE *age at onset*	MOLECULAR DIAGNOSIS
FSH Facioscapulohumeral muscular dystrophy	asymmetric weakness facial onset shoulder>>pelvic girdle humeroperoneal weakness no cardiac involvement	AD *10-30y*	deletions in 4qter • DNA studies • 10% new mutations • 10% non-4qter
OPMD Oculopharyngeal muscular dystrophy	ptosis dysphagia ± limb-girdle weakness late onset no cardiac involvement	AD *40-60y*	triplet expansions in PABP2 • DNA studies
EDMD Emery-Dreifuss muscular dystrophy	elbow, neck contractures humeroperoneal weakness cardiac conduction defects	X-linked (AD) *3-20y*	mutations in STA gene • absent emerin staining
Bethlem myopathy	finger,elbow contractures limb-girdle weakness no cardiac involvement	AD *0-50y*	mutations in collagen VI gene



OCULOPHARYNGEAL MUSCULAR DYSTROPHY (OPMD)

Late-onset ptosis (often asymmetric) and dysphagia are characteristic of OPMD in which ophthalmoplegia and limb-girdle weakness can also be present to a variable degree. The main differential diagnoses are myasthenia gravis, mitochondrial myopathy and myotonic dystrophy. Polymyositis and motor neuron disease can cause progressive dysphagia but not ptosis. OPMD is now known to be a triplet-repeat disease affecting a non-coding portion of the poly[A] binding protein 2 (PABP2) gene. The $[GCG]_n$ expansion differs from that seen in other neurological conditions in being short (8-13 repeats) and stable.

EMERY-DREIFUSS MUSCULAR DYSTROPHY (EDMD) and BETHLEM MYOPATHY

EDMD is characterized by the triad of (i) early contractures (especially in the elbows and neck); (ii) progressive humeroperoneal weakness and wasting; (iii) cardiac conduction defects. The flexed elbows and stiff neck so characteristic of the condition are not seen in BMD. Atrial paralysis with small or absent P-waves (leading to a sinus bradycardia) is almost pathognomonic of the condition and requires cardiac pacing. EDMD is usually X-linked and due to mutations of the STA gene which give rise to absence of the nuclear membrane protein emerin on immunohistochemistry.

Rare autosomal dominantly inherited EDMD is due to mutations in a different gene encoding lamins A and C. AD-EDMD has to be distinguished from Bethlem myopathy, another rare dominantly-inherited condition with prominent early contractures, particularly in the interphalangeal joints of the fingers and in the wrists and elbows. It is associated with mild limb-girdle weakness and the heart is not affected. Bethlem myopathy is caused by mutations in the gene for collagen VI.

Acknowledgements

The author would like to thank Muhammad Al-Lozi and Todd Devere for comments on an earlier version of this article; and Alan Pestronk and Andrew Kornberg (EDMD) for permission to reproduce photographs from http://www.neuro.wustl.edu/neuromuscular/.

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Correspondence Address

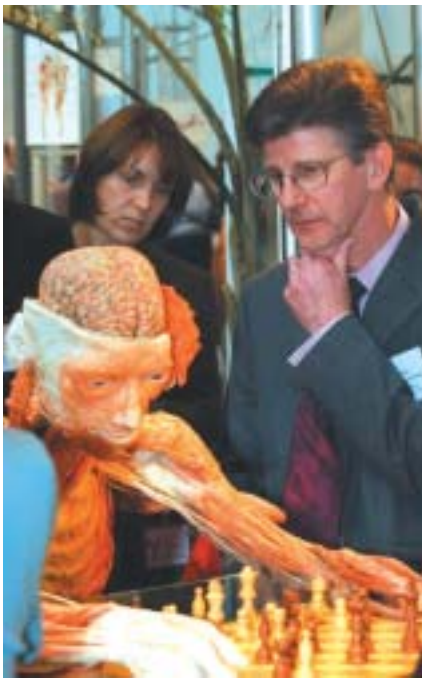
Dr Wojtek Rakowicz, Dept. of Neurology, Box 134, National Hospital for Neurology and Neurosurgery, Queen Square, London WC1N 3BG.
E Mail: adalbert@doctors.org.uk

Rivers of Fire - The untold story of neuropathic pain

27 August 2002, The Body Worlds Exhibition, London

Rivers of Fire was hosted by the Neuropathy Trust and held at the unusual but fascinating Body Worlds exhibition. Some of the country's leading diabetes, neurology and pain management specialists met with journalists at this important briefing to discuss the untold story of neuropathic pain.

The purpose of the meeting was to raise awareness of neuropathic pain amongst practitioners, via healthcare media, offering practitioners solutions for sharing both the management and the burden across both primary and secondary care.



Dr Steve Allen at the Body Worlds Exhibition in London

A Growing Concern

Tony Dickenson, Professor of Neuropharmacology at University College, London clarified the size of the issue:

- There are 2 billion chronic pain days world wide
- Chronic pain affects two thirds of people over 65
- There are over half a million sufferers of neuropathic pain in the UK.

Dr Steve Allen, a Pain Consultant from the Royal Berkshire Hospital discussed the burden of mismanagement of neuropathic pain. As one example, he cited the fact that patients with chronic pain use health services 5 times more than the general population.

Dr Solomon Tesfaye highlighted poor glycaemic control as one of the most common causes of neuropathic pain, and that since the incidence of diabetes is set to rise dramatically over the next few years, the incidence of painful diabetic neuropathy is set to rise with it. Interestingly, Dr Tesfaye noted that the tightening of glycaemic control might not relieve the pain once established.

According to Dr Simon Ellis, Consultant Neurologist and visiting Professor in Neuroscience at Staffordshire University, the number of neuropathic pain sufferers is set to increase to one million by the year 2010.

The Patient Perspective

Neuropathic pain has a profound impact on quality of life; leading in some cases to a myriad of secondary conditions including depression, sleep disturbance and impaired physical and psychological functioning.

Andrew Keen from the Neuropathy Trust gave a powerful insight into the real impact this level of suffering has on patients' lives. A history of misdiagnosis and long waiting periods for referral to pain clinics leads to years of private, hidden suffering.

So profound was the sense of frustration and helplessness that Andrew was motivated to establish the Neuropathy Trust. Andrew firmly believes that even a modest increase in the awareness of neuropathic pain and peripheral neuropathy amongst healthcare professionals could go a long way to alleviating this suffering.

What Help is Available?

Dr Allen explained that the main goals of therapy are to reduce the pain as much as possible, to support the patient in coping with this pain during therapy and to improve their physical mobility and quality of life. To achieve this, a rational treatment approach must be developed. He highlighted that:

- In recent years a number of neuropathic pain treatments have been proven effective in large-scale clinical trials, and licensed therapies do now exist.
- The tricyclic antidepressants have historically been a first line although they are not specifically licensed for the condition
- Anticonvulsants have also been used
- Gabapentin is licensed for the treatment of all types of neuropathic pain
- More complex cases of neuropathic pain may require a multi-modal approach including adjunctive therapies such as transcutaneous electrical nerve stimulation (TENS), acupuncture, reflexology and in severe cases cognitive behavioural therapy

He concluded by stating that "Education of all those involved to understand the abnormal physiology and to use appropriate therapies will lead to significantly improved patient care."

A Role for Primary Care

As was the case with Andrew Keen, most patients visit their GP as the first point of call. Dr Nigel Higson, A GP from Hove and Chairman of the Primary Care Virology Group, explained the varying levels of understanding of the condition that exists in general practice. He agreed that whilst a tremendous effort would be required for GPs to gain a deep understanding of neuropathic pain, they still have an extremely important role to play. In particular:

- Conditions such as trigeminal neuralgia, painful diabetic neuropathy and post herpetic neuralgia can and should be easily diagnosed in primary care
- These specific types of neuropathic pain can be treated with specifically targeted drugs
- Perseverance with traditional analgesics is rarely the answer
- Early referral to a pain specialist must also be considered when such treatment proves ineffective
- With increased awareness, and use of the appropriate course of treatment, GPs could achieve more for their patients, without necessarily increasing their workload
- When incorrectly managed the secondary symptoms such as sleep interference and depression are likely to increase a GP's workload

Dr Higson's final message to GPs was "If you can see it is neuropathic, treat it - if you can't treat it, see it as neuropathic."

The Neuropathy Trust is committed to a better future for all sufferers of peripheral neuropathy and neuropathic pain. Through education and communication to patients and healthcare professionals, the aim of the Trust is to raise awareness of these conditions and provide a lifeline to all suffers.

For more information on the Neuropathy Trust please visit www.neurocentre.com, email rof@neurocentre.com or alternatively or send a medium sized SAE to The Neuropathy Trust, PO Box 26, Nantwich, Cheshire, United Kingdom, CW5 5FP.

Rivers of Fire was sponsored by an educational grant from Pfizer Ltd. With thanks to the Body Worlds Exhibition for our front cover picture

Stem Cells: Prospects for Research and Therapy

11 September 2002, London, UK

Key Points:

- Stem cells hold considerable therapeutic promise, but much more research is needed before they can be considered for clinical application
- The MRC is leading a co-ordinating national stem cell strategy that involves other relevant Research Councils and charities, regulatory agencies, the scientific and clinical community, patients, the public and industry
- The first national stem cell bank is to be established at the National Institute for Biological Standards and Control (NIBSC) in Hertfordshire in order to allow both academic and clinical access to ethically approved and quality controlled stem cell lines from a variety of sources
- This MRC initiative, along with the prioritisation of government funding for stem cell research and favourable legislation, should place the UK in a leading position in this exciting area of science

Stem Cells: Prospects for Research and Therapy was held at the Millenium Gloucester Hotel in London, a very comfortable venue for what turned out to be an exciting and positive discussion about the future of stem cell-based therapies. The event was led by the Medical Research Council (MRC), and co-sponsored by the Biotechnology and Biological Sciences Research Council (BBSRC) and the Economic and Social Research Council (ESRC). It aimed to showcase UK developments in this new field, including the newly announced MRC-funded stem cell bank in Hertfordshire, which will be co-sponsored by the BBSRC and has full backing of the UK government. This bank will enable academic, clinical and industrial access to ethically sourced, quality controlled, new and existing stem cell lines of all types; adult, fetal and embryonic. A panel of highly distinguished speakers was present giving a varied perspective on the wide range of issues (including politics, ethics, religion, regulation and fundamental and clinical research challenges) that must be considered in order to promote activity in stem cell work in the UK. Approximately 400 delegates attended this high profile event, including members of the research and clinical communities, research councils, charities, patient groups such as the Parkinson's Disease Society (PDS) and the Alzheimer's Society, consumers, representatives from pharmaceutical companies and from pro-life groups plus the media.

Lord Sainsbury, the Minister for Science and Innovation introduced the meeting and gave an account of the investment being made by the government into science and the government's interest in the potential of stem cell research; he announced the creation of 12 new career development fellowships dedicated to this field of interest, which will be jointly funded by the MRC, BBSRC, Alzheimer's Society, Parkinson's Disease Society, Diabetes UK, plus the Juvenile Diabetes Research Foundation of America. Professor Sir John Pattison from the Department of Health (DOH) then gave a brief history of the development of legislation for stem cell research and indicated how the DOH plans to work closely alongside the MRC in order to promote the success of the stem cell bank. He discussed how the UK was becoming the obvious home for stem cell research, due to its existing research infrastructure, its promotion of stem cell research as a priority for funding and its balance of regulatory impositions. An overview of the UK stem cell initiative was given by Professor Sir George Radda, the Chief Executive of the MRC, who stressed the importance of collaboration, partnerships, co-operation and communication with a range of stakeholders. He also outlined the planned operation of the UK stem cell bank, how it will be funded and governed, including the appointment of a high level steering committee to be chaired by Lord Patel, and in general terms spoke about the practicalities of the facility, such as the banking of samples, quality control and the accessibility of cell lines from the bank. In addition, Professor Dr Ron McKay from the National Institute of Neurological Disorders and Stroke, Bethseda, USA, a international figure in the scientific stem cell arena, presented an elegant and considered overview of the potential of stem cells in research and therapy, and highlighted the scientific challenges facing the field.

The second session focused on governance of discovery and development and started with Mrs Suzi Leather from the Human Fertilisation and Embryology Authority (HFEA), who talked about how embryo donation for research will be controlled and the importance of informed donor consent.

The National Institute for Biological Standards and Control (NIBSC) in Hertfordshire, an agency that assures the quality of biological medicines, has been chosen as the home of the UK Stem Cell Bank. Dr Stephen Inglis and Dr Glyn Stacey from this facility described how they intend to manage the bank given their unique expertise in safety monitoring of human therapeutics, prior experience of cell-banking and experience in standardisation. Mrs Elizabeth Allanson from the Medicines Control Agency, the regulatory body that evaluates and accredits standards of Good Manufacturing Practice (GMP) in the UK, discussed a system of accreditation that should come into force in April 2003, that will provide the general public with the assurance that tissues and stem cells are handled in accordance with an appropriate quality control system. A clear message from these presentations was the high degree to which the success of the bank will depend on a two-way dialogue between the staff at NIBSC and the researchers and clinicians working with stem cells. The UK bank intends to store and make available non-GMP lines for basic research purposes and standardised GMP lines for use in clinical applications. Good practise controls will need to be implemented during the selection and retrieval of tissue, during testing and processing and finally during storage and delivery of the GMP lines to ensure consistency and quality; a monumental task given the inherent variabilities that exist! The morning session was concluded by some valuable and thought provoking discussions on the ethics and morals of stem cell research by Professors Ruth Chadwick from Lancaster University and Robin Gill from the University of Kent at Canterbury (both of whom were members of the MCR Stem Cell Bank Advisory Committee).

In the afternoon, the talks moved on to the importance of stem cells in basic research. Professor Nadia Rosenthal from the European Molecular Biology Laboratory in Monterotondo, discussed how the expression of insulin growth factor1 (*IGF1*) via a muscle specific transgene is able to mobilise stem cells in the bone marrow following injury to muscle, and how these stem cells can migrate specifically to the site of damage in order to induce some repair. Professor Cheryll Tickle (University of Dundee) highlighted the importance of basic developmental biology for enhancing our understanding of stem cells and their differentiation, since embryos are the natural environment of

stem cells and the construction of tissue and organs occurs here. Professor Roger Pederson, who moved from the USA to the University of Cambridge on an MRC International Appointment in order to continue to study embryonic stem (ES) cells, described his work with human ES cells, and in particular the definition of conditions that encourage them to differentiate into clinically useful cell types, for example, pancreatic b cells for the treatment of diabetes and cardiomyocytes for heart disease. The Director of Research and Development of the company Stem Cell Sciences UK, Dr Tim Allsopp, discussed the potential of human ES cells in high throughput screening for the purpose of drug discovery; in particular, the generation of healthy cells for research, healthy patient-specific cells for the treatment of disease and disease-specific cells for drug discovery.

The clinical session commenced with a presentation on haematopoietic stem cells, one of the most well characterised stem cell systems, by Professor Tony Green (Department of Haematology, Cambridge). In a series of very elegant studies he described how the position of the regulatory element (the +19 enhanceosome) for the stem cell leukaemia (SCL) gene (known to have an important role in the specification of haematopoietic stem cells, which give rise to all the cell types of the blood), was elucidated and the discovery that a complex of 3 proteins was required to bind to this key enhancer in order to activate it. This was followed by another presentation on the haematopoietic system from Dr Adrian Thrasher from Great Ormond Street Hospital, who went on to discuss how patients with severe combined immunodeficiency syndrome (SCID), have been treated with stem cells derived from the bone marrow that have been genetically modified to express the cytokine receptor gamma (gc) chain, a mutation in the gene of which causes X-linked SCID.

The potential for treatment of neurological diseases has been an area of intense interest and Professor Anne Rosser (University of Wales College of Medicine), described results of the ongoing MRC-funded trial of neural transplantation in Huntington's disease in the UK, and how the numbers of patients treated with this devastating inherited disorder could be vastly increased by the application of stem cells. Finally, Dr John Sinden, the Chief Scientific Officer at the company ReNeuron, discussed the development of stem cells lines from fetal and adult sources which he believes represent the the closest route to clinical application; he also announced that his company was keen to deposit such lines in the UK stem cell bank.

An anticipated highlight of the conference was a talk by the actor Christopher Reeve, to give the patient's perspective on stem cell research and treatment. This had been pre-recorded, but unfortunately on the day of the conference, the video failed to arrive, so a disappointed audience was treated to a few selected quotes from the transcript. Mr Reeve, having suffered a riding accident 7 years ago leaving him with severe spinal cord injury and quadriparesis, was quoted as saying "some people are able to accept living with disability, I am not one of them". "We should push politics and economics aside and let science proceed", he went on, demonstrating the devastation caused to the lives of patients suffering with such disabilities and the huge support for research to continue. Mrs Linda Kelly, the chief executive of the Parkinson's Disease Society, stepped in at short notice to speak eloquently about the work of the society and the importance of stem cells research to patients suffering with Parkinson's disease.

The meeting was concluded with an interactive question and answer session between the audience and the speakers in which a number of issues were raised; for example, about both the ethics and practicalities of embryo donation, about the merits of adult versus embryonic stem cells and about raising the expectations of the public too soon regarding the therapeutic outcomes of the research. Not often does a topic of scientific research lead to such prolific social, political and media interest, but overall one came away from this meeting with the feeling that, although there are still fundamental scientific questions to be addressed, and despite the considerable ethical concerns about some of the stem cell sources, there exists the political, social and scientific will to allow the potential of stem cells for the treatment of disease to be fully developed in years to come.

Meena Jain
(Centre for Brain Repair, Cambridge)
and Anne Rosser
(University of Wales College of Medicine, Cardiff)

Acknowledgements: The authors would like to thank Diane McLaren (MRC Head Office) for her helpful comments.

Further reading on stem cells:

Weissman IL *et al.* (2002). *Stem cells-scientific, medical, and political issues.* N.Engl.J.Med.346:1576-79
Prockop DJ (2002). *Adult stem cells gradually come of age.* Nature News and Views 20:791-2
Anderson DJ (2001). *Stem cells and pattern formation in the nervous system. The possible versus the actual.* Neuron 30:19-35
McKay R (2000). *Stem cells- Hype or hope.* Nature 406: 361-64
Weissman IL (2000).*Translating stem and progenitor cell biology to the clinic: barriers and opportunities.* Science 287:1442-46
Pedersen RA (1999). *Embryonic stem cells for medicine.* Sci Am. 280:68-73

Events Diary

If you would like your event listed in the next issue, send details to: Rachael Hansford on Fax: 0131 3131110 or E-Mail: AdvancesinCNR@aol.com by December 6th, 2002.

2002

November

32nd Annual Meeting of the Society for Neuroscience
2-7 November; Orlando, US
Tel. 001 202 462 6688, E. info@sfn.org

193rd Meeting of the Society for Endocrinology
4-6 November, 2002; RCP, UK
Tel. 01454 642 210, Fax. 01454 64222,
E. conferences@endocrinology.org

Approaches to the Skull Base
6-8 November, 2002; London, UK
Neurosurgery Courses Assistant, RCSE,
Tel. 0207 869 6335, Fax. 0207 869 6329,
E. neurosurgery@rcseng.ac.uk

Headache & Subarachnoid Haemorrhage
7 November, 2002; London, UK
RSM, Tel.l 020 7290 2984, E. cns@rsm.ac.uk

RCN Rehabilitiation Nurses Forum Annual Conference & Exhibition: Rehabilitation Nursing Skills
8-9 November, 2002; Bournemouth, UK
Elaine Sedgwick, RCN, Tel. 020 7647 3859,
Fax. 020 7647 3411, E.
elaine.sedgwick@rcn.org.uk

International Day for Creutzfeld-Jakob Disease
12 November, 2002; London, UK
Gillian Turner, Fax. 01630 673 993,
E. cjdnet@alzheimers.org.uk

Nikon Digital Imaging Seminar
12-14 November, 2002; Manchester, UK
Tel. Clare Williams on 0208 541 4440.

Core Skills in Neurosurgery
12-14 November, 2002; London, UK
Neurosurgery Courses Assistant, RCSE,
Tel. 0207 869 6335, Fax. 0207 869 6329,
E. neurosurgery@rcseng.ac.uk

Royal Hospital for Neuro-Disability Open Day
14 November, 2002; London, UK
Barney Johns, Tel. 020 8780 4500, E.
bjohns@rhn.org.uk

Section of Rehabilitation & Social Psychiatry Residential Meeting
14-15 November, 2002; Bournemouth, UK
Tel. 0207 2352 351 x 142,
E. pcornell2rcpsych.ac.uk

Managing Head & Neck Pain - European Cruise
11-24 November, 2002; Venice, Italy
Tel. 800 422 0711, Fax. 727 527 3228,
E. kciotti@continuingeducation.net

Parkinson's Disease & Movement Disorders
10-14 November, 2002; Florida, US
Tel. 414 276 2145, Fax. 414 276 2146,
E. kstanton@movementdisorders.org

Royal Hospital for Neurodisability Open Day
14 November, 2002; London, UK
Conference administrator, Royal Hospital for Neurodisability, Tel. 020 8780 4500 ext 5236, E. conferences@rhn.org.uk

Residential Meeting of the Section of Rehabilitation and Social Psychiatry
15-16 November, 2002; Newcastle, UK
Tel. 020 7235 2351,
E. rcpsych@rcpsych.ac.uk

13th International Symposium on ALS/MDN
17-19 November, 2002; Melbourne, Australia
Fax. 01 604 638 289,
E. symposium@mndassociation.org

AGM of the Vascular Surgery Society of Britain & Ireland
19-21 November, 2002; Harrogate, UK
Tel. 0207 9730 306, Fax. 0207 4309 235,
E. vssbgi@asgbi.org.uk

Risk 2002: Examining the Effective Management of Clinical Risk
20 November, 2002; London, UK
Healthcare Events, Tel. 0208 5411 399,
Fax. 0208 5472 300,
E. clare@healthcare-events.co.uk

Re-entry Into Real Life After Acquired Brain Injury: When Does Rehabilitation Finish?
22 November, 2002; London, UK
Tel/Fax. 020 8780 4569, E.
ukabif@rhn.org.uk

Symposium: Neurology
22 November, 2002; Edinburgh, Scotland
RCP, Tel. 0131 225 7324, Fax. 0131 220 3939.

BSRM Autumn Meeting: Practical Approaches to Managing Fatigue Problems in Rehabilitation
25 November, 2002; London, UK. Tel. 01992 638865, E. info@bsrm.co.uk

Assessing Rehab Potential
26 November, 2002; London, UK
Tel. RCP London on 020 7935 1174 x436,
E. conferences@rcplondon.ac.uk

Non-drug Treatment of Epilepsy in Childhood
27 November, London, UK
Tel. Melanie Armitage, RSM on 020 7290 3934, Fax. 020 7290 298.

International Meeting of Anaesthesia & Intensive Care
28-30 November, 2002; Portugal
Tel. 351 222 051 964, Fax. 351 222 004 294, E. jreis@chvng.min-saude.pt

Exploring Sexuality in Rehabilitation
29th November, 2002; Dundee, UK
Karen Girvan, Tel. 0141 620 0068, E.
karengirvanSSR@aol.com

December

SMART Introductory & Assessors Course
2-4 December, 2002; London, UK
Conference administrator, Royal Hospital for Neurodisability, Tel. 020 8780 4500 ext 5236, E. conferences@rhn.org.uk

2nd International Conference on Cerebral Amyloid Angiopathy
4-6 December, 2002; Newcastle, UK
Tel. Lise Hebert, Tel. 001 514 337 4646,
Fax. 001 514 337 5339, E. iccaa@neu-rochem.com

American Association of Neurological Surgeons/Congress of Neurological Surgeons (Paediatric section)
4-7 December, 2002; Phoenix, US
Tel. Lisa Sykes 847 378 0500, Fax. 847 378 0600, E. aansam@aans.org

Structural Specificity of the Motor Cortex
5 December, 2002; London, UK
E. j.townsend@ion.ucl.ac.uk,
www.ion.ucl.ac.uk/cgi-bin/seminars

Pituitary Disorders
5 December, 2002; London, UK
RSM, Tel. 020 7290 2984,
E. cns@rsm.ac.uk

Attention & Executive Skills
5-6 December, 2002; Ely, UK
Alison Gamble, Tel. 01353 652173,
Fax. 01353 652164,E-Mail.
alison.gamble@pow.lifespan-tr.anglox.nhs.uk

56th Annual Meeting of the American Epilepsy Society
6-10 December, 2002; Philadelphia, US
Fax. 8 605 867 550,
E. info@aesnet.org

Neural Information Processing Systems: Natural and Synthetic
9-14 December, 2002; Vancouver, Canada
Fax. 001 858 587 0417,
E. nipsinfo@salk.edu

Syndrome of Fixed Dystonia
10 December, 2002; London, UK
E. j.townsend@ion.ucl.ac.uk,
www.ion.ucl.ac.uk/cgi-bin/seminars

Dopamine Dysregulation Syndrome
10 December, 2002; London, UK
E. j.townsend@ion.ucl.ac.uk,
www.ion.ucl.ac.uk/cgi-bin/seminars

13th NECTAR Meeting (Network European CNS Transplantation And Restoration
12-14 December, 2002; Amsterdam, Netherlands
Fax. +31 20 696 1006,
E. g.boer@nih.knaw.nl

Head Injury: Long Term Outcomes
16 December, 2002; London, UK
Tel. Melanie Armitage, RSM on Tel. 020 7290 3934, Fax. 020 7290 298.

Joint Meeting of the Soceiete Francaise de Neuropathologie & Brtish Neuropathological Society
18-20 December, 2002; Southampton, UK
Stephanie Garfield,
E. stephanie.garfield@virgin.net or
Professor Roy Weller, E. row@soton.ac.uk

2003

January

Headache Now! 2003
17-19 January, 2003; Cancun, Mexico
Tel. 001 856 423 0043, Fax. 001 856 423 0082, E. ahshq@talley.com

4th Bessie & Louis Stein Geriatric Conference for Rehabilitation of the Elderly
19-21 January, 2003; Tel-Aviv, Israel
Prof G Friedman, Tel. 0097 226 777 627,
Fax. 0097 226 413 147,
E. friedman@hadassah.org.il

ANIM 2003
23-25 January 2003; Augsburg, Germany
Dr K Scheglmann, Tel. 00498 214 002 973,
Fax. 00498 214 002 691,
E. oa.neurologie@klinikum-augsburg.de

Neuromuscular Conference & EMG Workshop
25-26 January, 2003; London, Canada
E. betsy.toth@lhsc.on.ca

Neuroendoscopy
21-22 January, 2003; London, UK
Neurosurgery Courses Assistant, RCSE, Tel. 0207 869 6335, Fax. 0207 869 6329,
E. neurosurgery@rcseng.ac.uk

British Association of Stroke Physicians Annual Conference
22 January, 2003; Keele, UK
www.basp.ac.uk/baspconference2003.htm

ABN Joint Meeting with the Neurology Association of South Africa
29 January-1 February, 2003;
E. selliott@curie.uct.ac.za

Chicago Review Course in Neurological Surgery
31 Jan-9 February, 2003; Chicago, US
Tel. 001 773 296 6666,
Fax. 001 773 296 9999,
E. Dkeegan@chicagoreviewcourse.com

February

Quantitative Neurosciences: Models, Algorithms, Diagnostics, and Therapeutic Applications
5-7 February, 2003; Florida, US
E. Dr Panos Pardalos, pardalos@ufl.edu or Dr J Chris Sackellares, sackellares@epilepsy.health.ufl.edu

Gordon Holmes Prize for Trainees in Neurology, Neurosurgery, Neurophysiology, Neuropathology or Neuroradiology
6 February, 2003; London, UK
RSM, Tel. 020 7290 2984, E. cns@rsm.ac.uk

Neurological Anatomy
10-12 February, 2003; London, UK
Neurosurgery Courses Assistant, RCSE, Tel. 0207 869 6335, Fax. 0207 869 6329,
E. neurosurgery@rcseng.ac.uk

28th International Stroke Conference
13-15 February, 2003; Phoenix, US
Tel. LaRita Edwards, 001 214 706 1100,
Fax. 001 214 706 5262,
E. strokeconference@ heart.org

Neuroradiology
13 February, 2003; London, UK
Neurosurgery Courses Assistant, RCSE,
Tel. 0207 869 6335, Fax. 0207 869 6329,
E. neurosurgery@rcseng.ac.uk

Approaches for Intracranial Surgery
14 February, London, UK
Neurosurgery Courses Assistant, RCSE,
Tel. 0207 869 6335, Fax. 0207 869 6329,
E. neurosurgery@rcseng.ac.uk

2nd International Meeting on Steroids and Nervous System
22-26 February, 2003; Torino, Italy
Fax. 0039 0 116 707 732,
E. giancarlo.panzica@unito.it

Relevance of Cell Death in Development of Disease of the Brain
24-25 February, 2003; Berlin, Germany
Sonia Waiczies, Tel. 0049 30 450 539 051,
Fax. 0049 30 450 539 906,
E. sonia.waiczies@charite.de

Annual Conference on Acute Medical Emergencies
24-25 February, 2003; London, UK
Jayne Wesley-Smith, Tel. 0207 7200 600,
Fax. 0207 7207 177,
E. ame@confcomm.co.uk

Apomorphine treatment: A nurse's perspective

Sister P McGee

Background

Apomorphine is structurally similar to dopamine and is a potent agonist at both D_1 and D_2 type dopamine receptors. It is administered parenterally as a treatment for advanced Parkinson's disease (PD). The drug has been licensed since 1993 for use in PD patients with disabling motor fluctuations, resistant to manipulation of oral drug treatment. Apomorphine is given via a subcutaneous infusion pump, or APO-go pump. The timings of the pump are tailored to the patient's waking day, with daily infusion durations commonly ranging between 12 and 16 hours. It is not recommended that an apomorphine infusion pump be left on for 24 hours as this may cause localised swelling and irritation (there are quite a few patients who are on 24 hour infusions). This, in turn, can lead to nodules and scarring (figures 1 and 2). Apomorphine may also be intermittently administered subcutaneously by penject, or APO-go pen. This treatment is helpful for unpredictable off periods, providing a means of rescue within 5 to 15 minutes of administration.

The Apomorphine Challenge Test

The required dose of apomorphine is ascertained by an apomorphine challenge test. We use the Shared Care Guidelines produced by University College Hospital as our apomorphine challenge test protocol. The challenge is necessary to determine that the patient has a positive response to apomorphine, to establish the dose required to produce this response, and to identify their susceptibility to potential side effects such as postural hypotension, hallucinations, nausea or excessive somnolence. We usually perform the challenge test as a pre-planned day case admission, having previously written to the GP asking them to prescribe domperidone (normally 30 mgs tds for 72 hours prior to the admission). The patient is requested to withhold their anti-Parkinson's treatment from 12 midnight the night before admission. I have found that patients on longer acting oral dopamine agonists e.g. cabergoline should, if possible, withhold the agonist for at least 48 hours, as this may interfere with the result of the challenge test.

Patients are normally admitted as a day case around 9am, to avoid unnecessary prolongation of the off period. It is our usual practice to write to the GP prior to the patient's admission to establish whether they would agree to the on-going prescription of apomorphine, should the challenge test be successful. The GP is provided with extensive information about the drug and also the guarantee that the Consultant and I will oversee and monitor the therapy. We ensure that this agreement is obtained before the patient is brought up to hospital. Since this protocol was instituted, we have had few problems with GPs declining to prescribe apomorphine.

Starting Treatment with Apomorphine

Intermittent subcutaneous injection

If the patient is to use an APO-go pen, I normally instruct the carer/partner/patient on how to use this pen while conducting the apomorphine challenge test. I also give them a video provided by Britannia, instructing them how the pen works. Patients usually pick this up very quickly, as the pen is easy to use. There are problems with the design of the pen, however; some patients may find it difficult to administer the dosage as this requires the application of significant pressure to push the plunger down. This can be difficult in an OFF period. I always suggest that they have an injection prepared to avoid such problems. Patients and carers can also find it alien to initiate the apomorphine on an "as required" basis rather than at specific times. Commonly asked questions are "How long a gap do I leave between my tablets and an injection?" and "How many times a day can I use the pen?"

Continuous Subcutaneous Infusion

Once we have a positive test, I contact the District Nurse that will be responsible for putting on and taking down the infusion pump on a daily basis. I provide them with information regarding the use of apomorphine and its side effects. We also consider the implications for their service. Our area is a mix between urban and rural areas, where one District Nursing team may cover a large geographical area, sometimes making it difficult to regularly start the infusion at the most appropriate time for the patient.

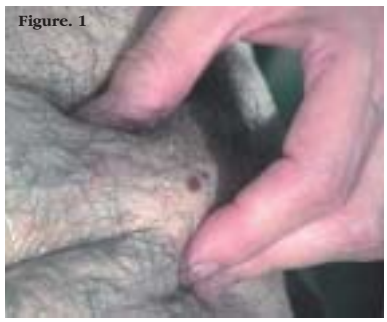
Patients going on to a pump are usually admitted to our neurological ward for a short stay. This is mainly to titrate or reduce other drug treatments and monitor the effectiveness of the apomorphine. The drug management depends on whether the patient will be given the apomorphine for bradykinesia and rigidity or for its anti-dyskinetic effect. In either instance, I aim to simplify the patient's medication regime as much as possible. On discharge, the patients are closely followed up and monitored to make sure any changes are appropriate.

The aim for patients prescribed apomorphine for their dyskinesias is to reduce the levodopa treatment as far as possible. It may be possible to run them on apomorphine "monotherapy" supplemented by a dose of dispersible levodopa in the morning before the pump is started and a controlled release preparation at night, or a combination of controlled release and dopamine agonist. Apomorphine infusions may also occasionally be used at night to control severe tremor, inadequately controlled on oral medication and associated with insomnia.

Training and Educational Issues

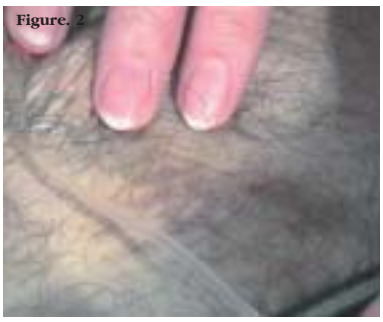
Training district nurses or nursing homes in the use of APO-go pumps can be time-consuming. As the area that I cover is fairly large, this often means travelling to rural parts, where I aim to train as many nurses from the relevant team as possible. I also try to identify a "link nurse" or district nursing sister who will then go on to cascade this training down to other staff at a later date. I use a step-by-step guide on setting up the apomorphine infusion pump and leave this at the patient's house, together with a copy of the Shared Care Guidelines booklet and my contact details. On the first day of discharge I arrange to see the patient at home with their carer and the district nurse. This is usually appreciated by the nurse and also gives me a chance to anticipate any early problems that might occur.

Figure. 1



Scarring associated with apomorphine treatment

Figure. 2



Nodule related to chronic apomorphine therapy

(Pictures: Courtesy of Britannia Pharmaceuticals Ltd)

Once I have taught carers, district nurses or nursing home staff on how to use an APO-go pump, I use an objective sheet which is signed off to make sure that they understand how to perform the process of starting the apomorphine infusion and how to use the APO-go pump. This provides some proof that training was given and that the nominated person is proficient in using the pump. Both the district nurse and I keep copies of this sheet.

Should the pumps break down or need replacing, I always leave instructions on how to acquire another pump from Britannia Pharmaceuticals at the patient's home so that the district nurse, patient or carer can instigate this, should I be unavailable.

Skin and Tissue Care

I teach site rotation to reduce nodule formation. I encourage the district nurses to use a chart to record on a daily basis the previously used site, especially if there are several district nurses visiting one patient. There does not seem to be any way of predicting which patients are more likely to suffer from severe nodule formation; it does not, for example, clearly associate with their body mass index. The sites commonly rotated to are the lower abdomen and thighs. However, if patients are running into problems with nodule formation, I suggest upper abdomen and iliac fossa areas.

I also recommend CicaGel dressings, used in plastic surgery for keloid scarring. These dressings are available on FP10 prescription and are beneficial in reducing nodule formation. I give the patient a supply on discharge or leave them at the patient's home for the district nurse, with instructions on usage. I prefer to use them at an early stage rather than waiting until nodules become problematic. I also encourage the patient or district nurse to massage around the needle site after the removal of the needle at the end of the infusion. I do not normally suggest squeezing out the apomorphine, as this can lead to increased soreness or infection. Tea Tree Oil may be massaged around the needle site if the area is particularly painful after the needle has been removed. My experience of this is anecdotal, but the oil does seem to help; it is difficult to say whether the oil just helps the massaging technique or whether it is the antiseptic properties of the Tea Tree Oil. Patients are also referred for ultrasound treatment of nodules, although how much ultrasound to use and for how long has not been well researched, to the best of my knowledge.

Follow Up

Once the patient is established on an apomorphine infusion it really depends on their particular needs and problems as to how often they are formally seen. They are reviewed on a regular basis in our Movement Disorder Clinic. However, I see them on a more regular basis if they run into any difficulties. I also encourage queries from GPs, district nurses or nursing home staff so potentially major problems can be "nipped in the bud" at an early stage.

Conclusion

Apomorphine therapy is very time consuming for a Parkinson's Disease Nurse. As with all anti-parkinsonian treatments, apomorphine requires careful monitoring and observation for potential side effects. The benefits of apomorphine can, however, be tremendous to the patient and carer in restoring and improving quality of life.

Correspondence to:

Sister PH McGee, Parkinson's Disease Nurse Specialist, Regional Neurosciences Centre, Newcastle General Hospital, Westgate Road, Newcastle upon Tyne NE4 6BE Telephone: 0191 282 3282

"We would like to thank Britannia Pharmaceuticals for sponsoring this article".

EDITOR'S CHOICE

Adult neural precursor cells and brain repair

The role and capabilities of the endogenous adult neural precursor cells have been debated in recent years but a number of papers in the last couple of months are starting to provide clear answers. Two papers have now clearly shown that adult neural precursor cells (npc) in the rat brain can respond to ischaemic lesions involving the striatum and hippocampus. Arvidsson and colleagues in Lund in a paper in Nature Medicine have shown that middle cerebral occlusion induces npc migration into the striatum (although interestingly not the overlying cortex) where they differentiate into the appropriate neuronal phenotype. However, it is not clear how successful such a reparative response is, in terms of the number of neurons generated and whether this is sufficient to alter behaviour.

The second paper is in Cell by Nakatomi *et al* and is a real tour de force, demonstrating that adult npc can lead to the regeneration of hippocampal pyramidal cells after an ischaemic insult (although other neurons were seen at other sites). These authors demonstrate that the cells can migrate to the hippocampus where they differentiate into the new neurons as evidenced by morphology, connectivity and neurophysiologically and that this has a functional consequence to the animal. Furthermore manipulation of the system using neurotrophic factors and anti-mitotic agents influences this response. This paper therefore demonstrates the capacity of adult npc to respond to ischaemic insults using a range of different methods and approaches and thus sets a new standard for such studies as well as offering hope for the future as a therapeutic approach.

Finally a paper by Theo Palmer *et al* has shown that neurogenesis can be adversely affected by cranial irradiation, probably by altering the environment in which the npc finds itself. This in turn may have consequences for understanding the sequelae of childhood irradiation and systemic chemotherapy in terms of cognitive deficits - a point that at the present time remains conjectural and unproven.

Therefore it is becoming clear that adult npc can respond to some injuries and mediate repair and that preventing their normal turnover may have significant consequences, although the extent to which this applies to man and the range of insults that the adult CNS is subject to remains to be discovered. ***- RAB***

Arvidsson A, Collin T, Kirik D, Lindvall O.
Neuronal replacement from endogenous precursors in the adult brain after stroke.
NATURE MEDICINE
8:963-970.

Nakatomi H, Kuriu T, Okabe S *et al.*
Regeneration of hippocampal pyramidal neurons after ischemic brain injury by recruitment of endogenous neural progenitors.
CELL
2002 110:429-441.

Monje ML, Mizumatsu S, Fike JR, Palmer TD.
Irradiation induces neural precursor-cell dysfunction.
NATURE MEDICINE
2002 Sep;8(9):955-62.

NEUROTOXINS

Nanging and Neurology

A case report from New Zealand provides an additional cause for sub acute combined degeneration of the spinal cord. This condition arises as a result of vitamin B12 deficiency, which leads to deficient production of myelin phospholipids. The dorsal columns bear the brunt of the insult but other components of the spinal cord and peripheral nerves are also involved leading to myelopathy, peripheral axonal neuropathy, with parasthesiae, gait ataxia, sphincter disturbance and pyramidal weakness. Cognition and levels of anxiety may also be affected. These were the features that the subject of this case report presented with. The eventual cause of the Vitamin B12 deficiency in this 37-year-old man, after other possible causes were excluded, was excessive inhalation of nitrous oxide. Replacement treatment with parental vitamin B12 produced resolution of the symptoms.

What is interesting with this case report is the insight into nitrous oxide inhalation, which is the commonest inhaled agent of abuse. A common source of the nitrous oxide is capsules used to produce whipped cream, which are readily available from supermarkets and hardware stores. The sound distortions produced after inhaling nitrous oxide are referred to as "nanging". The cobalt atom in vitamin B12 is irreversibly oxidised by nitrous oxide effectively producing a Vitamin B12 deficiency. ***-TH***

Ng J, and Frith R.
Nanging.
LANCET
2002; 360:384

ALZHEIMER'S DISEASE

★★★ RECOMMENDED

IVIg for Alzheimer's disease?

Intravenous immunoglobulin (IVIg) is used in the treatment of several neurological disorders presumed to have immune-mediated pathogenesis. This paper suggests that Alzheimer's disease (AD)

might join the list. Previous studies by these authors have shown that human serum and CSF contains IgG antibodies directed against the amyloid €peptide (A€which accumulates in plaques in AD brain. The role of such antibodies is uncertain, but they may contribute to immune-mediated clearance of A€, which is itself a normal constituent of CSF with possible physiological roles. AD patients have lower levels of anti-A€antibodies compared to controls.

In the current study, a specific ELISA was used to show that antibodies recognising A€ were present in two commercially available IVIg preparations. Patients (n = 7) who received IVIg for a variety of neurological indications (MS, peripheral neuropathy, LEMS, dermatomyositis) were shown to have reduced CSF total A€ and A€$_{1-42}$ and increased CSF anti-A€ antibodies after treatment as compared to baseline. Serum total A€ and anti-A€ antibodies both increased, with a non-significant trend toward increased serum A€$_{1-42}$, after treatment, suggesting the possibility of increased antibody-mediated clearance of A€ from CSF to serum.

Although very preliminary, these findings do tally with observations in AD transgenic mice, where anti-A€ antibodies given passively or following immunisation with A€have been shown to reduce A€ deposition and prevent decline in some aspects of (mouse) cognitive function. Whether such a therapeutic approach will translate to the clinical arena remains to be seen. ***-AJL***

Dodel R, Hampel H, Depboylu C *et al.*
Human antibodies against amyloid €peptide: a potential treatment for Alzheimer's disease.
ANNALS OF NEUROLOGY
2002;52(2):253-256

STUTTERING

Persistent stuttering: a neuro-anatomical explanation

Up to 5% of all children suffer from stuttering but the vast majority of these cases resolve spontaneously. In the 1% of people suffering from stuttering that does not spontaneously remit during puberty very little has been known about the anatomy of this disorder. Diffusion tensor imaging (DTI), a MRI technique, uses the diffusion properties of water to determine the orientation of white matter tracts. Using powerful analysis techniques associated with DTI such as fractional anisotropy of diffusion and voxel based morphometry white matter tract myelination abnormalities have been detected in patients with multiple sclerosis. So using DTI, this current study tried to define the anatomical pathology of persistent stuttering. DTI of 15 patients with persistent stuttering was compared with images of 15 normal controls. Of all the participants only one patient in the stuttering group was left-handed. A significant difference between the two groups was observed in the area immediately below the laryngeal and tongue representation in the left sensorimotor cortex. This area has fibre tracts, which connect the premotor cortex (planning motor aspects of speech) with the sensorimotor representation of the oropharynx (articulation). Therefore the authors suggest that the normal temporal pattern of activation from the premotor to the motor cortex is disrupted. Previous PET studies on persistent stutterers have demonstrated an overactivation in the right hemisphere. In this study no structural abnormalities in the right hemisphere were demonstrated therefore allowing the authors to further speculate that this activation is not a cause of the stuttering but rather compensation for the structural damage in the left hemisphere. Such compensation has been demonstrated in aphasia. ***-TH***

Sommer M, Koch M, Paulus W, Weiller C, Buchel C.
Disconnection Of Speech-Relevant Brain Areas In Persistent Developmental Stuttering.
LANCET
2002; 360: 380-83

EPILEPSY

★★★ RECOMMENDED

Hairy stories about antiepileptic drugs in pregnancy

If doctors are worried about the teratogenic effects of anti-epileptic drugs, it is nothing to what patients feel. It has long been suspected that women becoming pregnant stop medication and that this is a major cause of loss of control of epilepsy during pregnancy. This is no trivial issue since in the last confidential enquiry into maternal deaths, epilepsy was the second commonest cause (19 of 134 deaths).

Hair from the vertex grows at 1 cm per month. Drugs are sequestered into hair from the circulation and leech out from the hair in a linear and predictable fashion over time. In this study Williams *et al* took (cut not pulled) samples of hair from the vertex of 26 pregnant and 13 control patients. They cut them into 1 cm segments, corresponding to months of gestation and analysed them for lamotrigine and carbamazepine. They saw three patterns. First normal, minor fluctuations in drug levels. Second major variability suggesting fluctuating compliance and third withdrawal pattern in which levels declined as pregnancy progressed. Self-discontinuation affected 15% but was not generally associated with withdrawal seizures or deteriorating control. Patients usually denied altering intake.

There is a bitter irony in this study that discontinuation after the patient realises they are pregnant will not prevent the more major malformations from occurring, although more minor developmental and cognitive consequences of these drugs remain open to question. In one tragic case, a woman suffered a sudden unexplained death in epilepsy (SUDEP) during pregnancy. Analysis of her hair, including at post mortem revealed that she had been taking her medication consistently; further evidence that SUDEP is generally not due to poor compliance. ***-MM***

J Williams, V Myson, S Steward, G Jones, JF Wilson, MP Kerr, PEM Smith.
Self-discontinuation of antiepileptic medication in pregnancy: detection by hair analysis.
EPILEPSIA
2002;43:824-31

PARKINSON'S DISEASE

A novel approach to treating parkinson's disease

A fascinating and provocative paper in Science uses a gene therapy approach to change the phenotype of neurons in the subthalamic nucleus and by so doing not only ameliorate features of PD in the animal model but appears to convey neuroprotecton. In this study Luo *et al* injected adeno-associated viral vectors containing the gene for glutamic acid decarboxylase (GAD), the enzyme involved in the synthesis of GABA, into the subthalamic nucleus (STN) of rats. This was not associated with any host immune response several months after injection when the gene was still present, but was associated with a successful switch in phenotype of the STN neurons from glutamergic to GABAergic. This structure is the major nucleus driving the outflow of the basal ganglia (see ACNR 2.4., pp9-10) and in Parkinson's disease (PD) the STN is thought to be overactive which explains the beneficial effects of deep brain stimulators and lesioning of this nucleus in advanced cases of this condition. Thus by changing the output from this nucleus from an excitation to inhibition, one would expect a benefit in terms of the signs of experimental PD - and this is indeed the case. So far so good, but this study has made one other observation and that is, that this change in phenotype actually protects nigral dopaminergic neurons from toxic damage with 6-OHDA - something that is not seen in cases where the STN is actually destroyed. In other words an inhibitory input from the STN to the substantia nigra protects cells, whilst no input - or if

you like, the lack of an excitatory input is without effect, suggesting that inhibition is necessary for cell rescue. This is remarkable, and although no explanation is given to account for this it is nevertheless of great interest. Thus this paper takes a well researched approach using viral vectors but uses a novel target and strategy which produces unexpected results...and as such may have profound implications for how we think about neuroprotecting the parkinsonian brain ***-RAB***

Luo J, Kaplitt MG, Fitzsimons HL *et al* (2002)
Subthalamic GAD gene therapy in a Parkinson's disease rat model.
SCIENCE
2002 298: 425-429.

REHABILITATION

Good vibrations for the treatment of unilateral neglect

Unilateral neglect hinders the rehabilitation of many people with right hemisphere brain damage. As treatment, therapists often try to encourage patients to look left and practice visual scanning tasks. However such training tends to be very task specific with gains shown only in the practiced tasks and even these improvements are only seen when patients have some awareness of their problem. Recently new treatments, which challenge the integration of vision, and other orienting systems that use proprioceptive or vestibular inputs, have reported successful results in the literature. It is thought that these treatments somehow recalibrate the egocentric coordinate system that is responsible for the localisation of the body in space and of object position in relation to the body. One such treatment is neck muscle vibration, which perturbs both proprioceptive inputs and vestibular inputs that are important for building up representations of head position. A crossover study reported in the Journal of Neurology, Neurosurgery and Psychiatry by Schindler *et al.* has shown beneficial effects that generalised beyond the tasks practiced and were long lasting.

After a three week baseline 20 patients with unilateral neglect were given visual exploration training using a computer for 30 sessions. For the first 15 sessions half of the patients had their posterior neck muscles on the contralesional side stimulated with a vibrating disc while they were doing the training programme; the other half had visual exploration training only. After that the groups swapped treatments for the next 15 sessions. Perception of midline and exploration deficits in both visual and tactile modalities were tested. In addition patients were assessed on a reading task and their carers were given a questionnaire to rate the incidence of everyday problems relating to neglect. Reduction in symptoms of neglect was achieved in both the trained visual and untrained tactile exploration mode after training combined with neck vibration. Reading performance improved and the incidence of everyday problems also reduced. The improvement was still evident two months after completion of the treatment. In contrast visual exploration training alone resulted in only small benefits in visual exploration. There was no significant transfer effect to other tasks.

These results are good news especially since the treatment is easy and inexpensive to apply and does not require patients to have awareness of their condition. ***–AJT***

Schindler I, Kerkhoff G, Karnath H-O, Keller I, Goldenberg G
Neck muscle vibration induces lasting recovery in spatial neglect.
JOURNAL OF NEUROLOGY, NEUROSURGERY AND PSYCHIATRY
2002: 73: 412-419

Good Posture

Postural muscles are constantly battling against the relentless effects of gravity whenever we decide to stand upright. This balancing act has to contend with any motor action we may decide to perform, always maintaining the postural equilibrium. Movements that threaten our stability are commonly accompanied by anticipatory changes in the activity of postural muscles and the CNS generates these patterns in a feed forward manner before the onset of the perturbation. Studies of these anticipatory postural adjustments (APAs) have been shown in healthy individuals to be affected by 3 major factors: expected magnitude and direction of the perturbation, voluntary action associated with the perturbation, and current postural state. These anticipatory and compensatory mechanisms have been shown to be impaired in patients with stroke. Slijper and colleagues have confirmed this in their recent study but have also addressed the influence of a light manual support and the effects of changing the direction of the perturbation. A heterogenous group of stroke patients including cortical and subcortical lesions were studied against a group of age-matched controls. All patients had their stroke at least 6 months prior to the test. Subjects were required to release a weight held in the extended arm, either in front of them or to the side. Surface electrodes measured the activity of muscles in the limbs and trunk. Experiments with a light manual support, a touchpad to rest the paretic hand upon, were compared without such aids. APAs were asymmetric in the stroke group with reduced activity on the paretic side, but perhaps of more interest were the signs of ineffective modulation of APAs on the 'non-paretic' side. Support conditions did not seem to improve matters. It appears to be the case that the CNS in the patient with a hemiparesis avoids excessive use of muscles in the affected limb even when the task requires it, i.e. when subjects released the weight from the contralateral side. Successful rehabilitation needs to consider optimising these APAs, which if not corrected may in time become maladaptive, making the patient less able to cope with an ever-changing environment. ***-JLR***

Slijper H, Latsh ML, Rao N and Aruin AS.
Task-specific modulation of anticipatory postural adjustments in individuals with hemiparesis.
CLINICAL NEUROPHYSIOLOGY
2002: 113: 642-655

STROKE

How to find the hole in the heart?

Ten to 30% of the normal population harbours a patent foramen ovale (PFO). In young (<55 yrs of age) patients with ischaemic stroke a significant proportion are "cryptogenic", ie after an adequate search no definite cause for the stroke was found. Of these up to 40-50% may have a PFO - but it is uncertain whether the PFO was relevant or not.

We now know, from a carefully-designed European prospective follow up study of patients with cryptogenic stroke, that the risk of recurrent stroke (whilst taking aspirin) with an isolated PFO is around 0.5% per annum, and that if there is an associated atrial septal aneurysm (ASA) the risk rises to about 4% per annum. As yet we do not have clinical trial evidence to guide us as to whether antiplatelet therapy, anticoagulation or endovascular closure are the best and safest ways of preventing stroke recurrence. Trials are in the process of being set up.

The historical "gold standard" for detecting PFOs has been transoesophageal echocardiography (TOE) with echocontrast and a right to left shunt may be demonstrated during the Valsalva manoeuvre. However it is often difficult for the stroke patient to perform a Valsalva when they have a TOE camera down their throat. False negative tests may thus result.

The alternative is to use transcranial Doppler (TCD) with echocontrast and monitoring for air microembolic signals in the middle cerebral artery (MCA) during Valsalva. This approach gets around the mechanical problem of Valsalva during TOE but is less specific in that there is no direct visualisation of the shunt at cardiac level. The operator must follow strict guidance on the appearance of MCA microembolic signals within 10-15 cardiac cycles. Appearance of signals beyond this time is suggestive of shunting

at another site (usually a pulmonary arteriovenous fistula).

This article is a succinct review of the pros and cons of looking for PFOs using either method. This is becoming an increasingly important consideration and given how simple the TCD method is to perform it would seem reasonable to use TCD for screening and TOE perhaps for confirmation in TCD positive cases. ***-PJM***

Baguet JP, Besson G, Tremel F, Mangin L, Richardot C, Mallion JM.
Should one use Echocardiography or Contrast Transcranial Doppler Ultrasound for the detection of Patent Foramen Ovale after an Ischaemic Cerebrovascular Accident?
CEREBROVASCULAR DISEASES
2001;12:318-324

Botox for stroke spasticity

It stands to reason that if spasticity in the muscles of the wrist and fingers after stroke contributes to disability then local treatment with intra-muscular botulinum toxin type A (Botox) should provide improvement. But the evidence base for this is limited. In a multicenter randomised double blind placebo-controlled trail comparing once-off set of Botox injections (200-240 units) into the wrist and finger muscles with placebo involving 126 patients, this issue was addressed. Patient eligibility in this study was a stroke, at least six months prior to randomisation, resulting in increased flexor tone in the hand or finger. Baseline assessment included patient choice of the most personally relevant disability (choice of 4 possibilities: pain, personal hygiene, dressing and limb position), and investigator rating of flexor tone. At six weeks post injection 62% of patients in the Botox group reported a significant improvement in their chosen disability compared to 27% improvement in the placebo group. This observed benefit was sustained for at least 12 weeks and in an open label extension phase of this study the Botox benefit persisted with subsequent injections and lasted for up to 24 weeks in some patients. Investigator-observed spasticity also differed between the experimental groups providing evidence that the Botox was physiologically active. So with the observed decrease in spasticity, and reported improvement in ability, the working hypothesis has been shown to hold true. No adverse events were noted. Interestingly one of the patients in the Botox group who did not experience any improvement had Botox neutralising antibodies in post treatment serological analysis. Unfortunately baseline levels of the neutralising antibodies in this patient were not determined eliminating the obvious physiological explanation for the observed treatment failure. This study goes a long way to offer hope that some help to relieve disability can be offered to patients with significant spasticity of the hand after stroke. ***-TH***

Brashear, A, Gordon, M, Elovic, E, Kassicieh, D, Marciniak, C, Do, M, Lee, C, Jenkins, S, Turkel, C for the Botox Post-Stroke Spasticity Study Group.
Intramuscular injection of botulinum toxin for the treatment of wrist and finger spasticity after a stroke.
NEW ENGLAND JOURNAL OF MEDICINE
2002; 347:395-400

Sexual Intercourse and the risk of Stroke

There has been little good science investigating whether sexual activity can cause stroke either acutely or over a long period of time. Some reports have linked haemorrhagic stroke with sexual activity, and there have been reports of increased risk of sudden death following vigorous exertion, although there is hitherto little known about the relationship between increased sexual activity and risks of ischaemic stroke.

Whether increased frequency of sexual intercourse increased or decreased risk for ischaemic stroke and coronary heart disease (CHD) was examined in this study. The Caerphilly study is an ongoing cohort study which has collected prospective information regarding multiple known and putative cardiovascular risk factors at the outset and recorded cardiovascular events over the subsequent 20 years. Men aged 45-59 were divided into 3 groups on the basis of their frequency of sexual intercourse at the start of the study. Less than once a month was described as 'low frequency'; twice or more a week was described as 'high frequency', and the remaining men were put into an 'intermediate' group. Disappointingly, rates of ischaemic stroke were slightly lower for those men engaging in less frequent sexual intercourse, although no significant pattern was seen after adjustment for age, and known cardiovascular risk factors.

Interestingly, stroke was most common among those men who did not respond to the question on sexual activity, and these men tended to be older, shorter, and had a higher level of CHD at the start of the study. In contrast however, fatal heart attacks were observed more commonly among men with infrequent sexual activity. (Data regarding haemorrhagic stroke was not described presumably due to low numbers).

Although this study cannot explore the relationship between sexual activity and the triggering of an acute stroke, it should provide some reassurance for middle aged men that sexual activity is not a strong risk factor for ischaemic stroke, and may even protect against heart attacks. ***-TF***

Ebrahim S, May M, Ben Shlomo Y, McCarron P, Frankel S, Yarnell J, Davey, Smith G.
Sexual intercourse and the risk of ischaemic stroke and coronary heart disease: the Caerphilly study.
JOURNAL OF EPIDEMIOLOGY AND COMMUNITY HEALTH
(2002) 56:99-102

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E-Mail.arnoldjournals@hodder.co.uk,www.arnoldpublishers.com/journals

Current Opinion in Neurology
Lippincott Williams & Wilkins, 241 Borough High Street, London, SE1 1GB. Tel 0207 940 7564, Fax 0207 940 7530
Email. rmclachl@lww.co.uk, www.Lww.co.uk

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www.blackwellscience.com/epi

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- Targeted relief of spasticity without the sedation of oral agents[3, 7]
- A low protein formulation means a low chance of an antigenic response[5, 6]

References:
1. Brashear et al, 2001.
2. Gordon et al, 2002.
3. Ward et al, 2001.
4. Barnes, 2001.
5. Goschel H, 1997.
6. Hatheway CL, Dang C, 1994.
7. Ko Ko, Ward, 1997.

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Nikon is pleased to introduce the C1 confocal microscope system – a new ultra compact and lightweight system that supports a variety of imaging techniques including simultaneous 3-channel fluorescence plus diascopic DIC, time-lapse recording and spatial analysis.

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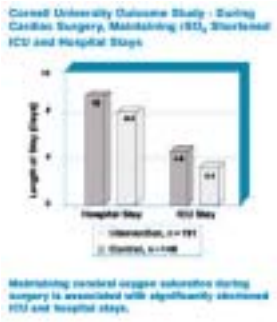
LabLogic

Maintaining brain oxygen saturation during cardiac surgery shortened hospital stays



A study from the Weill Medical College of Cornell University demonstrated that maintaining regional brain oxygen saturation at adequate levels during cardiac surgery shortened ICU and hospital stays.

The patients were monitored with Somanetics' INVOS Cerebral Oximeter, the only commercially-available patient monitoring system to noninvasively and continuously monitor changes in the regional blood oxygen saturation in the brain.

Use of this patient monitoring system allows medical professionals to monitor changes in cortical blood oxygen saturation and take corrective action. Research indicates that such action can prevent or reduce neurological injuries related to surgery and other critical care situations, and reduce the associated cost of care.

The intervention group experienced a lower incidence and duration of brain oxygen desaturation, and had significantly shorter ICU and hospital stays than the control group. On average, ICU stays were shortened by one and a half days and hospital length of stay was reduced by about two days, thus reducing the total costs of surgery.

For more information contact Tyco Healthcare Ltd on Tel. 01329 224226, E-Mail. marketing@tycohealth.com

INTERNATIONAL CJD DAY

Tuesday November 12, 2002 is International CJD Day - the aim is to raise public awareness of this very rare disease.

To mark the day a one-day conference, "Aspects and Perspectives", is being held at The Glaxo Neurological Centre, Liverpool, 9.30am-4.15pm. Zoey Appleyard will release balloons in memory of those people who have died with CJD in the last ten years, and a rose will be launched, Nina Nadine, specially cultivated in memory of people who have died. The CJD Support Network will also launch CJD Nursing Guidelines, and the Brain & Spine Foundation will launch a CJD information pack.

Speakers include Dr Angus Kennedy, Consultant Neurologist; Prof JW Ironside, Consultant Neuropathologist,/Director of the National CJD Surveillance Unit; Dr M Doran, Consultant Neurologist; Dr A Larner, Consultant Neurologist; Professor Don Jeffries, Vice President, The Royal College of Pathologists, Vice Chair CJD Incidents Panel; Mr R Tomkins and Ms S Shadbolt.

On Sunday November 17 at St Martin in the Fields, a memorial service will be held at 6.30pm to remember people who have died with CJD.

For further information visit www.cjdsupport.net

Integrating theory and practice in neuropsychological rehabilitation

The Oliver Zangwill Centre run an annual programme of workshops for professionals involved in the rehabilitation and care of adults with brain injury. Adrian McGrath, Forensic Psychologist and Psychotherapist HM Prison, Altcourse, Liverpool, attended a workshop which focused on the integration of theory and practice in relation to neuropsychological rehabilitation.

"The workshop provided participants with a comprehensive knowledge of various theoretical models and how these may be applied in guiding clinical formulation and interventions. Cognitive, emotional and neuropsychological formulations were emphasised and the day culminated in participants working in small groups to apply their knowledge of specific frameworks with a specific case example.

The clinical implications of working with brain injury require practitioners to develop and maintain their knowledge of a variety of frameworks by incorporating evidence-based models and methodologies from a number of different fields. Various models of emotional sequelae of brain injury were explored. I would highly recommend these workshops to other professionals working with brain injury or with other clinical work involving cognitive deficits, for example, schizophrenia."

For more information contact Alison Gamble, The Oliver Zangwill Centre, Tel: 01353 652173, E-Mail alison.gamble@pow.lifespan-tr.anglox.nhs.uk

Ultra-high field MR

Obtaining new insights into the functions and metabolic processes of the brain is one of the reasons for research institutions and hospitals to invest in ultra-high field magnetic resonance (MR) systems. Siemens Medical Solutions offers two different 3T (Tesla) models for neurological examinations. Siemens also provides the primary components for 7T systems used primarily for research.

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Magnetic resonance (MR) systems compute diagnostic images. However, various types of noise are superimposed on the signal. To obtain an optimal signal, either the signal must be increased or the noise eliminated. The solution is to increase signal intensity by applying stronger magnetic fields. As a result, 3 tesla and (later) 7 tesla MR systems were developed.

Initially, MR systems with strong magnetic fields required a great deal of space, making them very costly for hospitals. Today's modern magnet design means that 3 Tesla systems require no more space than current 1.5 Tesla systems.

Clinical Applications

Information as to how individual regions of the brain function is critical. By measuring the BOLD effects (Blood-Oxygenation-Level-Dependent), conclusions may be drawn on which neuronal regions in the brain are active. Ultra high-field MR is the tool for comprehensive mapping of the human brain.

MR spectroscopy enables metabolic changes in the brain to be displayed. This information can be used to determine the activity of tumours, plaque, multiple sclerosis, or epilepsy. Because of the higher signal produced, 3T MR spectroscopy enables more precise and reliable spectral analysis.

For more information contact Mike Bell on Tel. 01344 396317, or see www.siemensmedical.com

Ebixa® for Alzheimer's disease

Data on Ebixa® (memantine), the first and only agent in a new class, and the only agent indicated for moderately severe to severe Alzheimer's disease, was presented recently by Lundbeck. Clinical trials of this NMDA (N-methyl-D-aspartate) receptor antagonist have demonstrated benefits in global response (overall improvement), function (activities of daily living) and cognition (memory and thought processes).

This benefits patients and carers since patients may be less dependent, potentially delaying admission to long-term care. There was also a reduction in time spent by carers.

Ebixa® represents a new opportunity to treat moderately severe and severe Alzheimer's disease. There are no other agents available for the severe stage of Alzheimer's disease, yet 75% of the treatment costs relate to this stage.

Ebixa® works through a different mechanism than other currently approved Alzheimer's agents. It is an NMDA receptor antagonist, which protects the brain against excess glutamate, a messenger chemical released in excess amounts in brains suffering from Alzheimer's disease.

For more information tel. 01908 649966.

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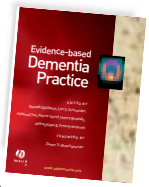

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Genetics and human behaviour: the ethical contex

Embryos should not be selected for behavioural traits such as intelligence on the basis of genetic information, according to a Report published recently by the Nuffield Council on Bioethics. The Report, Genetics and human behaviour: the ethical context, looks at ethical, legal and social issues raised by research into behavioural genetics.

Research to find out how our genes influence behaviour is complex and controversial. "This is a potentially explosive area," says Professor Bob Hepple, QC, Chairman of the Working Party and Master of Clare College, Cambridge, "and the first question we asked was whether such research should be carried out at all. We concluded that it can be justified because it has the potential to advance our understanding of human behaviour. However, it is important to create safeguards to protect against its misuse."

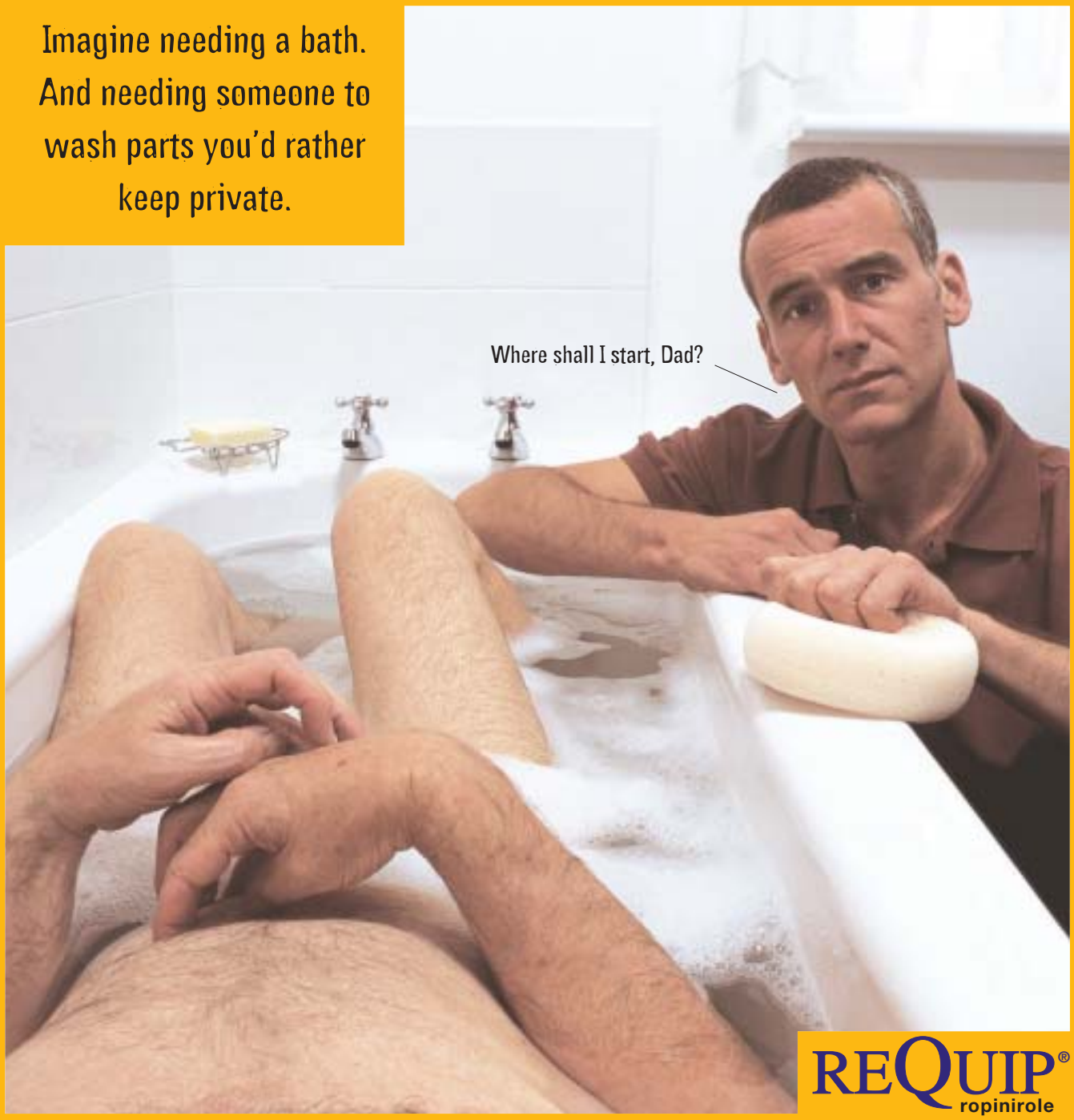
The Working Party assessed the evidence of associations between genetic variants and behaviour, considering traits such as intelligence, antisocial behaviour, personality traits and sexual orientation. Despite a number of highly publicised claims, no gene has been shown conclusively to influence antisocial behaviour, intelligence in the normal range, or sexual orientation.

"It is unlikely that variation in just one gene contributes to a trait", says Professor Hepple. "Many genes are likely to be involved and the environment also plays an important role. 'We should not overestimate the predictive power of genes,' he continues. "The effects of genes are not inevitable."

Copies of the Report can be downloaded from the Council's website, www.nuffieldbioethics.org

For a printed copy, E-Mail. bioethics@nuffieldfoundation.org, or Tel. 020 7681 9619.

Imagine needing a bath. And needing someone to wash parts you'd rather keep private.



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REQUIP (ropinirole) Prescribing Information
Presentation 'Requip' Tablets, PL 10592/0085-0089, each containing ropinirole hydrochloride equivalent to either 0.25, 0.5, 1, 2 or 5 mg ropinirole. Starter Pack (105 tablets), £43.12. Follow On Pack (147 tablets), £80.00; 1 mg tablets – 84 tablets, £46.20; 2 mg tablets – 84 tablets, £92.40; 5 mg tablets – 84 tablets, £184.80. **Indications** Treatment of idiopathic Parkinson's disease. May be used alone (without L-dopa) or in addition to L-dopa to control "on-off" fluctuations and permit a reduction in the L-dopa dose. **Dosage** Adults: Three times a day, with meals. Titrate dose against efficacy and tolerability. Initial dose for 1st week should be 0.25 mg t.i.d., 2nd week 0.5 mg t.i.d., 3rd week 0.75 mg t.i.d., 4th week 1 mg t.i.d. After initial titration, dose may be increased in weekly increments of up to 3mg/day until acceptable therapeutic response established. If using Follow On Pack, the dose for 5th week is 1.5mg t.i.d., 6th week 2.0mg t.i.d., 7th week 2.5mg t.i.d., 8th week 3.0mg t.i.d. Do not exceed 24 mg/day. Concurrent L-dopa dose may be reduced gradually by around 20%. When switching from another dopamine agonist follow manufacturer's guidance on discontinuation. Discontinue ropinirole by reducing doses over one week. Renal or hepatic impairment: No change needed in mild to moderate renal impairment. Not studied in severe renal or hepatic impairment – administration not recommended. Elderly: Titrate dose in normal manner. Children: Parkinson's disease does not occur in children – do not give to children. **Contra-indications** Hypersensitivity to ropinirole, pregnancy, lactation and women of child-bearing potential unless using adequate contraception. **Precautions** Caution advised in patients with severe cardiovascular disease and when co-administering with anti-hypertensive and anti-arrhythmic agents. Patients with major psychotic disorders should be treated with dopamine agonists only if potential benefits outweigh the risks. Ropinirole has been associated with somnolence and episodes of sudden sleep onset. Patients must be informed of this and advised to exercise caution while driving or operating machines during treatment with ropinirole. Patients who have experienced somnolence and/or an episode of sudden sleep onset must refrain from driving or operating machines. Caution advised when taking other sedating medication or alcohol in combination with ropinirole. If sudden onset of sleep occurs in patients, consider dose reduction or drug withdrawal. **Drug interactions** Neuroleptics and other centrally active dopamine antagonists may diminish effectiveness of ropinirole – avoid concomitant use. No dosage adjustment needed when co-administering with L-dopa or domperidone. No interaction seen with other Parkinson's disease drugs but take care when adding ropinirole to treatment regimen. Other dopamine agonists may be used with caution. In a study with concurrent digoxin, no interaction seen which would require dosage adjustment. Metabolised by cytochrome P450 enzyme CYP1A2 therefore potential for interaction with substrates or inhibitors of this enzyme – ropinirole dose may need adjustment when these drugs are introduced or withdrawn. Increased plasma levels of ropinirole have been observed with high oestrogen doses. In patients on hormone replacement therapy (HRT) ropinirole treatment may be initiated in normal manner, however, if HRT is stopped or introduced during ropinirole treatment, dosage adjustment may be required. No information on interaction with alcohol – as with other centrally active medications, caution patients against taking ropinirole with alcohol. **Pregnancy and lactation** Do not use during pregnancy – based on results of animal studies. There have been no studies of ropinirole in human pregnancy. Do not use in nursing mothers as lactation may be inhibited. **Adverse reactions** In early therapy: nausea, somnolence, leg oedema, abdominal pain, vomiting and syncope. In adjunct therapy: dyskinesia, nausea, hallucinations and confusion. Incidence of postural hypotension (commonly associated with dopamine agonists), was not markedly different from placebo, however, decreases in systolic blood pressure have been noted; symptomatic hypotension and bradycardia, occasionally severe, may occur. As with another dopamine agonist, extreme somnolence and/or sudden onset of sleep have been reported rarely, occasionally when driving (see 'Precautions' and 'Effects on ability to drive and use machines'). **Effects on ability to drive and use machines** Patients being treated with ropinirole and presenting with somnolence and/or sudden sleep episodes must be informed to refrain from driving or engaging in activities where impaired alertness may put themselves or others at risk of serious injury or death (e.g. operating machines) until such recurrent episodes and somnolence have resolved. **Overdosage** No incidences reported. Symptoms of overdose likely to be related to dopaminergic activity.

POM

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