LETTERS TO THE EDITOR

British neurology: a national focus

British neurology is held in especial high esteem by both domestic and international medical community. For over 100 years the natural focus for British neurological practice has been the National Hospital, Queen Square. It has played a leading part in the development of neurology as a descriptive science and has also served as a place of training in neurology for physicians and neurologists from both the United Kingdom and abroad. Most of the United Kingdom university chairs in neurology are currently held by neurologists trained at Queen Square.

In 1990, the Institute of Neurology was created to help develop academic neurology and encourage the evolution of the subject from a descriptive to a mechanistic science. In this task, the Institute has been singularly successful and has obtained consistently high ratings in the University Funding Council’s research exercises. The Hospital and Institute now have several internation-ally renowned groups with research focused on movement disorders, multiple sclerosis, neuro-oncology, neurogenetics, periphere nerve and muscle disease, dementia, neuropsychiatry, neuropsychology, and epilepsy. The recent award of £22 million by Wellcome Trust and the Leopold Muller Trust to the Institute to create both the Department of Cognitive Neurology and its PET unit with functional MRI, shows tremendous confidence in the Institute’s academic credentials. The application to common neurological disorders of the emerging technologies of molecular cell biology and molecular genetics has already provided valuable insights into our understanding of the causes of multiple sclerosis and the major neurodegenerative diseases. The benefits of this programme are already being reaped in the creation of new strategies to treat, for instance, Duchenne muscular dystrophy. We believe that the National Hospital and the Institute of Neurology have a pivotal part to play in developing, elaborating, and promoting these advances as well as in training neurologists in their application.

The recent denial of Trust status to the National Hospital has brought into sharp focus the complexities of providing a clinical neuroscience service in the 1990s. Neurological practice is continuing to evolve and the National Hospital is at the leading edge of this process. Neuroimaging by CT and MRI provide but one example of the extent to which new methods have revolutionised inpatient and outpatient neuro- logical care. The increase in neurological units in the United Kingdom has established additional centres of excellence. The advent of the new health care market has added a further dimension of uncertain- ty that will impinge on the service provided at Queen Square.

There is a growing appreciation, how- ever, that neurology and neuroscience are entering a new and exciting phase of deve- lopment. We believe in the principle that the nature of the neurological specialties require that they have a national focus for clinical practice, research, and training. This will maintain the cohesiveness of the specialties and will serve to provide a centre for clinical neuroscience research. An adequate flow of patients is required to serve both of these commitments. Today’s market forces demand that this flow be secure and provide a sound financial foundation for clinical services and training. The Neurology shows that these advances have a physically integrated clinical and basic neuroscience research facility of appropriate size, and be in close association with multidisciplinary clinical and academic services.

We suggest that regardless of any politi- cal or financial considerations, there is a unique opportunity to create a major neuro- logical institution of national and interna- tional stature to assimilate the various facets of clinical and academic practice in neuro- logy and the neurosciences. The principal purpose and function of this initiative are clearly identified. The National Hospital and Institute of Neurology look forward to contributing to the new era of British clinical neuroscience. The heritage of “Queen Square” must be valued and its future secured through a clarity of purpose, not to protect, but to develop, expand, and enrich its role and authority.

A H V SCHAPIRA
Department of Clinical Neurosciences, Royal Free Hospital School of Medicine, and University Department of Clinical Neurology, Institute of Neurology and National Hospital for Neurology and Neurosurgery, London, UK

CD MARSDEN
University Department of Clinical Neurology, Institute of Neurology and National Hospital for Neurology and Neurosurgery, London, UK

A unique case of dystrophinopathy

Becker and Duchenne dystrophies are allelic X-linked diseases—the first mild, the second severe—characterized by a gene deletion on the long arm Xp21.1 Dystrophin, a 427-kilodalton protein, is absent in Duchenne and present although abnormal in Becker dystrophy.2 Other signs of Becker muscular dystrophy are progressive symmetric muscular weakness, a more than five-fold increase in serum creatine kinase, myopath- ic electromyography (EMG), and muscle biopsy characterised by a variable fibre diameter, foci of regenerating fibres, presence of necrotic fibres, and variable increase in connective and fat tissue.3 Blood creatine kinase is high from birth, whereas other signs of the disease appear in late childhood or adolescence; patients remain ambulant beyond the age of 16.

We report abnormal expression of dystrophin with gene deletion in a male child, who at birth presented bilateral diaphragm paralysis, generalised muscle weakness, and ptosis of the eyelids. Other features were a prominent forehead, broad and flat nasal root, hypertelorism, low-set ears, high arched palate, and bilateral cryptorchidism. After correction of the respiratory acidosis, exhaustion plasma and urine tests, including lactate and pyruvate, amino acids, organic acids, carotidines, lysosomal enzymes, and creatine kinase had normal values, and repeatedly so; as were the chromosomal map, abdominal ultrasound, brain NMR, acoustic evoked potentials, electrocardio- gram and echocardiogram, and the results of the sweat test, 51Cr-labelled red blood cell and an autoantibody titre of 1:4 to dystrophin. Muscle biopsy at three months led to diagno- sis of congenital myopathy with type II hypertrophy. Muscle immunostaining with a panel of antibodies to different antigenic regions of the dystrophin molecule showed patchy dystrophin distribution on the surfaces of muscle fibres with five antibodies, whereas dystrophin localisation seemed greatly reduced using the anti-D8 antibody.4 Western blotting showed a dystro- phin band of reduced molecular weight and intensity. Analysis of peripheral blood genomic DNA by a multiplex polymerase chain reaction protocol failed to detect exons in the deletion prone “hot spot” regions of the dystrophin gene, showed deletion of exons 49-52.5 Exon 53 was found deleted by Southern blot analysis.6 Muscular (with immunocytochemical and immuno- blot analyses) and blood DNA analysis were repeated at 13 months with identical results: in particular the muscle did not pre- sent dystrophin bands.

The clinical condition of the child improved gradually although he needed a respirator for 20 months. At the most recent check up, at 33 months, he was able to walk and climb actively (although he has mild hypotonia), but could not talk. He is mentally retarded and of short stature. The child is the second of non-consanguineous parents, the sister has mild mental retardation. Plasma creatine kinase and EMG were normal in both parents and muscle biopsy was normal in the father. In the mother fibre size varied considerably but immunostaining showed dystrophin located normally. From analysis of DNA polymorphisms the probability of the moth- er being heterozygous for the gene defect was estimated at 80%.

This is a puzzling case presenting Becker-like dystrophinopathy from the molecular and immunohistological point of view but with normal blood creatine kinase and no clinical signs of muscular dystrophy, although there is congenital myopathy with mental retardation.

The financial support of Telethon, Italy to M Mora and F Cornelio is gratefully acknowledged.

F DWORZAK M MORA L MORANDI P BERNASCHINI F CORNELIO Division of Neuro muscular Disorders, Istituto Neurologico “C. Besta”, Via Celoria 11, 20133 Milan, Italy

Correspondence to: Dr Federica Dworzak, Division of Neuromuscular Disorders, Istituto Neurologico “C. Besta”, Via Celoria 11, 20133 Milan, Italy.


An "n of 1" trial of intravenous immunoglobulin treatment for chronic inflammatory demyelinating polyneuropathy

One small double blind study has found intravenous immunoglobulin (IVIG) to be effective in chronic inflammatory demyelinating polyradiculoneuropathy (CIDP).1 We describe an "n of 1" trial in a patient who received IVIG and who considered that "it worked".

In 1968, when 37 years old, the man developed transient upper limb paraesthesiae. In 1970, these symptoms returned in both hands and feet together with muscle soreness in the left foot with balance. Examination showed weakness of ankle dorsiflexion, slight intention tremor of the upper limbs, areflexia, and glove and stocking sensory loss. The CSF protein was 1.9 g/l, 30% of which was γ globulin. No cells were present. Peripheral nerve conduction velocities were reduced. The next year he developed sensory loss below the knees. Treatment with prednisolone was started and the response was striking. In 1978, azathioprine was added. His subsequent course was characterised by relapses and remissions superimposed on a slow but progressive decline. In 1989, an intravenous infusion of IVIG (0.4 g/kg/day) was given for five days. Limb function improved considerably so that he no longer used a walking stick. The same dose was repeated every three weeks until November and then withheld for the next six months during which the patient's walking deteriorated. Subsequent treatment with IVIG (0.4 g/kg/month) again seemed successful, prompting a formal evaluation in September 1990. A double blind placebo controlled single patient study was divided into four sequences of treatment, each consisting of four infusions, two placebo and two active (figure). Each infusion was given once every three weeks over 48 (4 x 4 x 3) weeks. The placebo was albumin and the study preparation was IVIG (0.4 g/kg) given over about two hours. Before the study started and immediately before each infusion, a standardised neurophysiological assessment was made. The outcomes were (a) time to walk 10 metres, (b) maximum number of squats in 30 seconds, (c) maximum range of ankle dorsiflexion, and (d) the patient's opinion as to whether he had received IVIG or placebo. The patient declined repeated nerve conduction studies. He continued to take prednisolone (20 mg) on alternate days and azathioprine (50 mg per day).

There was no definite treatment effect objectively. The probability that the patient would correctly identify the treatment on 11 or more of the 14 occasions, however, was significant (p = 0.03 (one sided test)). The lack of a major treatment effect could reflect the lack of a simple, reliable, valid, and communicable measure of outcome. The time to walk 10 metres and the number of squats in 30 seconds, although objective, are insensitive and have a definite "ceiling" effect, particularly as the patient had only mild proximal weakness. Perhaps we should have timed his walking over a longer distance. The range of ankle dorsiflexion is subject to considerable within and between observer variation. Possibly the best indicator was the patient's own opinion (he was correct on all but three occasions) but it could be argued that this was not a patient blind assessment because some patients describe a "kick" soon after receiving IVIG.

Whether the lack of effect in this patient reflected the concurrent use of immunosuppressives; the severity of CIDP; the patient's "burnt out" disease with little capacity for recovery; the possibility that he may have responded to IVIG at one time, but not at another, becoming more refractory to any form of treatment as the disease advanced; the fact that he was a real "non-responder"; or we were mistaken and the patient was correct, remains unknown. Nevertheless, this study illustrates some of the difficulties that will be encountered in any randomised controlled trial, notwithstanding the considerable expense of the treatment and the time and effort it took to perform even an "n of 1" trial.

If a large trial were to be undertaken, a prespecified hypothesis should be that subgroups of patients with CIDP exist (some may respond to IVIG and others not). More importantly, better measures of outcome are necessary; patients may have different types of disability, and the accurate assessment of each demands more thought than we anticipated. Although neurophysiologically based studies are objective they may not reflect function and may not be tolerated. Perhaps the Rankin scale is the most appropriate simple and reliable measure of functional outcome, despite being relatively insensitive. After all, if a treatment as costly as IVIG is going to be used, it should improve function by a degree that could be detected on the Rankin scale.

Peripheral neuropathy associated with dialysis amyloidosis

Haemodialysis associated amyloidosis1 also called β2 microglobulin amyloidosis2), a novel type of secondary amyloidosis, is a frequent complication in patients with chronic renal failure on prolonged maintenance haemodialysis with cuprophan membranes for 10 years. After eight years on dialysis she developed weakness and numbness and dysaesthesia in the lower extremities. In August 1992, she was admitted to our hospital for evaluation of these symptoms. Her medical history and family history were unremarkable. Cranial nerves and autonomic function were normal. There was distal weakness and wasting of the lower but not of the upper limbs. Sensory examination showed distal and symmetric hypoesthesia in the lower limbs, involving all modalities of sensation. Tendon reflexes were normal at the knees and absent at the ankles. There were no pathologic reflexes, no signs of carpal tunnel syndrome, and no signs of systemic amyloidosis.

Routine blood tests were normal. Serum β2 microglobulin concentration was 86-4 mg/l (Pharmacia radioimmunoassay; normal <3 mg/l). There was no Bence-Jones proteinuria or a monoclonal immunoglobulin on serum protein electrophoresis. Moderate amounts of long duration polyphasic high amplitude motor units were found by EMG in the muscles of the lower limbs. The motor nerve conduction velocity

7 The outcomes of which could be considerable within and between observer variation. Possibly the best indicator was the patient's own opinion (he was correct on all but three occasions) but it could be argued that this was not a patient blind assessment because some patients describe a "kick" soon after receiving IVIG.
8 Whether the lack of effect in this patient reflected the concurrent use of immunosuppressives; the severity of CIDP; the patient's "burnt out" disease with little capacity for recovery; the possibility that he may have responded to IVIG at one time, but not at another, becoming more refractory to any form of treatment as the disease advanced; the fact that he was a real "non-responder"; or we were mistaken and the patient was correct, remains unknown. Nevertheless, this study illustrates some of the difficulties that will be encountered in any randomised controlled trial, notwithstanding the considerable expense of the treatment and the time and effort it took to perform even an "n of 1" trial.
9 If a large trial were to be undertaken, a prespecified hypothesis should be that subgroups of patients with CIDP exist (some may respond to IVIG and others not). More importantly, better measures of outcome are necessary; patients may have different types of disability, and the accurate assessment of each demands more thought than we anticipated. Although neurophysiologically based studies are objective they may not reflect function and may not be tolerated. Perhaps the Rankin scale is the most appropriate simple and reliable measure of functional outcome, despite being relatively insensitive. After all, if a treatment as costly as IVIG is going to be used, it should improve function by a degree that could be detected on the Rankin scale.
10 Peripheral neuropathy associated with dialysis amyloidosis
11 Haemodialysis associated amyloidosis also called β2 microglobulin amyloidosis, a novel type of secondary amyloidosis, is a frequent complication in patients with chronic renal failure on prolonged maintenance haemodialysis with cuprophan membranes for 10 years. After eight years on dialysis she developed weakness and numbness and dysaesthesia in the lower extremities. In August 1992, she was admitted to our hospital for evaluation of these symptoms. Her medical history and family history were unremarkable. Cranial nerves and autonomic function were normal. There was distal weakness and wasting of the lower but not of the upper limbs. Sensory examination showed distal and symmetric hypoesthesia in the lower limbs, involving all modalities of sensation. Tendon reflexes were normal at the knees and absent at the ankles. There were no pathologic reflexes, no signs of carpal tunnel syndrome, and no signs of systemic amyloidosis.