

## LETTERS TO THE EDITOR

### Anosognosia for hemiplegia after a brainstem haematoma: a pathological case

The pathogenesis of anosognosia for hemiplegia (AHP) remains unclear, but recent theories have involved global cognitive deterioration or more modular mechanisms.<sup>1-3</sup> Persistent AHP is usually found in left hemiplegic patients with large right frontoparietal cortical lesions or with subcortical damage, specially to the perithalamic regions.<sup>1-4</sup> Anosognosia for motor deficit is exceptionally reported in "non-hemispheric" damage and is related to a simultaneous confusional state.<sup>5,6</sup> We report a patient with severe and prolonged anosognosia for left hemiplegia occurring after a right pedunclopontine haemorrhage. A possible explanation for this AHP might be the association of a left complete somatosensory deficit secondary to brainstem lesion with a global cognitive impairment due to histologically established Alzheimer's disease. This case, to our knowledge, is unique in the literature and it raises interesting questions on the origin of AHP.

An 83 year old right handed woman was admitted to hospital because she was found confused with a left hemiplegia. She had an history of hypertension treated with a salidiuretic. She had lived alone since the death of her husband, 15 years ago, and was taking good care of herself, despite a moderate impairment of memory for recent events noticed by her daughter since the past two years. On admission, she was lethargic with a blood pressure of 185/105 mm Hg, a complete proportional left motor and sensory deficit, a discrete right peripheral facial paresis, a conjugate gaze deviation to the left, and swallowing difficulties. Brain CT showed a right lateralised pontine haemorrhage. The mental confusion decreased progressively and disappeared at the end of the second week after onset, allowing a full participation in examination. During the third and fourth weeks after onset, the left hemiplegia remained stable. The patient was unable to detect any type of sensory stimuli when applied on her left side, whereas answers elicited from the right side were normal. There was no sign of left spatial hemineglect or left hemiasomatognosia: the patient performed a perfect midline bisection, and she was able to point on command with her right hand to various parts of her extrapersonal space and of her body. She expressed no delusion of absence or ownership of body parts. She scored from 16 to 19/30 on Folstein's mini mental state examination (MMSE), depending on her fatigue. At the same time she was totally unaware of her deficit, as we showed repeatedly with Starkstein's anosognosia questionnaire.<sup>2</sup> She never reported her sensorimotor deficit spontaneously. When asked about the reasons for her stay in hospital, she would evoke a check up ordered by her physician. Non-oriented questions about her health would obtain similar answers. She could see no reason that could restrain her ability to walk, except some degree of

fatigue. To any specific question directed towards the presence of a sensory or motor deficit, she would always report none. When asked to move her left arm or leg, she would move the right limb instead. When the deficit was directly shown to her, she would never acknowledge it or show any emotional reaction. She would usually say that she was too exhausted to move any more. At the same time, when asked if a person with one paralysed side would be able to walk, she would answer that, of course, it was impossible with such a deficit. From weeks 5 to 7 after onset, the patient's condition continued to improve. The MMSE score was consistently about 22/30. She scored 117/144 on the Mattis dementia rating scale (attention 32/37; initiation/perseveration 26/49; construction 3/6; conceptualisation 33/39; memory 20/25). Somatosensory deficit was unchanged, whereas the left motor deficit improved slightly in her left arm. Brain MRI performed during the fifth week after onset, showed no associated focal hemispheric lesion other than the haematoma, but bilateral white matter hyperintensities (T2 sequences) in the high frontal periventricular regions. During the same period, the patient never reported her deficit in the following situations: casual conversation, following a general question, or after specific questions regarding her limb strength or feeling. When confronted with the reality of the deficit, she would sometimes admit that she was not able to walk, and that her left limbs were "a little bit stiff". A few minutes later she would manifest no concern about her deficit. Conversely, she repeatedly questioned the resident about her blood pressure, and complained about the inconvenience due to the loss of her glasses. We did not assess with a formal questionnaire<sup>3</sup> the presence of anosognosia to cognitive deficits, but we noticed that the patient acknowledged (but never reported spontaneously) mild memory disturbances and cognitive slowing. She twice received a psychiatric assessment that showed a slightly blunted affect, with no depression or anxiety. The patient died suddenly during the eighth week after onset. Necropsy showed that death was due to bilateral pulmonary embolism. Her brain weighed 1210 g. The left temporal lobe showed a moderately atrophic aspect. There was no focal cortical or subcortical lesion in the cerebral hemispheres. A 1cm wide haematoma was found in the right rostral pons extending from the caudal midbrain to the middle pons (figure). We performed the usual histological staining (haematoxylin-eosin, Bodian silver, Luxol fast blue, and Congo red) and an immunohistochemical analysis of A $\beta$  and tau proteins. Lesions of Alzheimer's disease were found in all the cortical areas, characterised by numerous A $\beta$  positive amyloid plaques. Neurofibrillary tangles were rare in the isocortices, but were numerous within hippocampic (mostly in CA2) and entorhinal cortices on both sides. Neuronal loss was more severe in the left CA1 subarea, but was symmetric elsewhere.

We describe a patient with a mild Alzheimer's disease who had a lateralised brainstem lesion and developed subsequently a severe and long lasting AHP, in all points similar to that described in right hemispheric damages. This AHP contrasted with a very mild anosognosia to cognitive deficits and normal concerns with other medical problems. We found no associated cortical or subcortical infarction, specially in the right parietal, fron-



Serial cuts of the brainstem showing a haematoma extending from the right ventrolateral part of the caudal midbrain to the right upper midpart of the pons.

tal, or perithalamic regions, nor myelinic pallor such as described in microvascular hypertensive pathology. The brainstem lesion obviously caused the patient's motor and somatosensory deficits, but cannot by itself explain the AHP. Hemisensory loss (specially proprioception) is necessary for persistent AHP, but not sufficient.<sup>1</sup> The initial confusional state did not last long enough to cause the AHP, as proposed in other reports.<sup>5,6</sup> A feed forward deficit<sup>3</sup> is not an appropriate explanation, as the lesion site would not cause a motor neglect (postulated as the main factor of AHP in this hypothesis), and because the AHP remained almost unchanged when the motor deficit started to improve. The patient's death prevents us from knowing whether a greater recovery would have overcome the anosognosia. The patient showed no behavioural particularity that could contribute to the AHP;<sup>7</sup> she presented no visuo-verbal confabulation nor delusion, and psychiatric examination disclosed no depression or specific attitude toward illness.

We think that this unusual AHP could result from the association in the same patient of a stroke and Alzheimer's disease through a special pattern of cognitive deficit. Levine *et al* have reported several patients with pre-stroke dementia who sustained hemiplegia and had no AHP.<sup>1</sup> These patients, however,

had no hemisensory loss. Starkstein *et al*<sup>2</sup> have shown that cognitive deficits are not necessary to produce AHP but could constitute a contributing factor in some patients. In our patient, is not clear whether the AHP was due to a global or to a specific cognitive impairment. We think that a global reduction of attentional resources cannot explain the AHP in this case, given the specificity of the anosognosia. We could not relate AHP to a degraded body scheme, a hemispatial neglect, or a hemiasomatognosia. The memory deficit was mild, without confabulatory tendency, and it would not explain the AHP by a difficulty of remembering the newly acquired hemiplegia. Some theories of unawareness posit that AHP could be, at least partly, related to some mental inflexibility or to deficits in self monitoring and internal representation.<sup>1,2</sup> Such deficits are usually associated with damage to the frontal lobes or to frontal-subcortical circuits. In our patient, the analysis of the Mattis scale subscores showed a prominent frontal dysexecutive syndrome. This peculiar cognitive pattern may have been of some importance in the appearance of AHP in the patient. Starkstein *et al*<sup>2</sup> have proposed two domains of anosognosia in Alzheimer's disease, cognitive and behavioural. Based on this very unusual case, we think that anosognosia to non-cognitive non-behavioural deficits might represent a third domain that should be assessed systematically in patients with mild Alzheimer's disease with a stroke. Such studies might be very useful to the understanding of mechanisms of anosognosia.

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### Opsoclonus as a paraneoplastic manifestation of pancreatic carcinoma

Opsoclonus refers to involuntary, repetitive, and disorganised rapid conjugate eye movements in all directions of gaze.<sup>1</sup> The diagnosis is usually a clinical one as, strictly speaking, it requires the demonstration of no intersaccadic interval on oculography.<sup>2</sup> It may be associated with myoclonus of the trunk and limbs and cerebellar dysfunction.<sup>3</sup> Opsoclonus can occur at any age, and has been associated with numerous neoplastic conditions, including neuroblastoma in children and breast, lung, uterine, ovarian, and thyroid carcinoma, and Hodgkin's disease in adults.<sup>4-6</sup> It has not previously been reported as a paraneoplastic phenomenon associated with carcinoma of the pancreas.

A 70 year old man, with a past medical history of hypertension and osteoarthritis, presented with a 10 day history of intermittent vomiting and increasing gait unsteadiness. He complained of vertigo, which was worse on standing, and ataxia, falling to the right. There was no history of headache, neck stiffness, photophobia, blurred vision, deafness or tinnitus. Prior to his presentation to hospital, he had been commenced on promethazine by his local doctor, with no effect on his symptoms. Other medications at this stage included perindopril and indapamide for hypertension, and aspirin. He drank only 20 g (two standard drinks) of alcohol a day and ceased smoking one year previously, after a 25 pack-year history. The only neurological signs on examination were nystagmus to the right on horizontal gaze and an unsteady gait. Brain CT showed age related cerebral atrophy, with no infarction. A provisional diagnosis of vestibular neuronitis was made, and he was started on 500 µg clonazepam twice a day.

Over the next four days, he remained nauseated and vertiginous. He then developed a left upper motor neuron facial weakness, left upper limb clumsiness, left ptosis, bidirectional nystagmus, and dysarthria. A provisional diagnosis of a brainstem infarct was made, intravenous heparin started, and a cerebral MRI organised. The next day, his pupils were small but equal and reactive, and there was a partial left lateral rectus palsy. His visual axes were disturbed with left over right hypertropia. Opsoclonus was present with involuntary, repetitive, and disorganised rapid conjugate eye movements in all directions of gaze. Speech and swallowing were unimpaired, and there were no long tract signs. The cerebral MRI showed atrophic changes in the deep white matter of both hemispheres, but no other abnormalities.

One week later he was still nauseated, and had developed past pointing on the right more than the left, with an action tremor of his hand. He now had a complete left lateral rectus palsy and the left upper motor neuron facial weakness had recurred. Opsoclonus was still evident. Power and deep tendon reflexes of his upper limb were normal.

A lumbar puncture showed a CSF protein of 0.66 g/l, with 30 × 10<sup>6</sup> mononuclear cells and no polymorphonuclear cells. Paraneoplastic antibodies were not detected in the serum or in the CSF.

The patient's overall condition deteriorated over the next few days and he required nasogastric feeding. Episodes of respiratory distress, possibly as a result of aspiration, became more frequent and he died two days later.

A postmortem disclosed an occult 3 cm multiloculated cyst in the tail of the pancreas. The morphological diagnosis was primary large duct adenocarcinoma of the pancreas. There was also a 6 cm subcapsular hepatic nodule consistent with a metastasis from a pancreatic primary. There was no macroscopic evidence of cerebral haemorrhage, infection, or infarction. Microscopically, there was perivascular lymphocyte cuffing in the upper medulla, pons, midbrain, thalamus, and hippocampus, with some microglial proliferation and gliosis. This finding was thought to be consistent with a paraneoplastic meningoencephalitis.

We think that this is the first case to be reported in the literature of a paraneoplastic opsoclonus syndrome secondary to carcinoma of the pancreas. The syndrome has, however, been reported in association with other malignancies. Opsoclonus is considered to be due to an abnormality of omnipause neurons in the pontine paramedian reticular formation (PPRF), which are involved in the tonic inhibitory control of horizontal and vertical saccadic eye movements.<sup>7</sup> The actual site may be within the PPRF or in descending pathways to the PPRF through the midbrain.

The patient had a macroscopically normal pons, midbrain, and cerebellum at postmortem. Microscopically however, there was perivascular lymphocyte cuffing in the upper medulla, pons, midbrain, thalamus, and hippocampus, with some microglial proliferation and gliosis. The perivascular lymphocyte cuffing, microglial proliferation, and gliosis in the pons could explain the dysfunction of the omnipause neurons in the PPRF. This abnormality may therefore provide a theoretical explanation for opsoclonus in this case.

An autoimmune basis to the syndrome has been suggested, but there seems to be insufficient evidence to support this.<sup>8-10</sup> Paraneoplastic autoantibodies, anti-Purkinje cell antibodies (anti-Yo), and the antineuronal nuclear antibodies type 1 (anti-Hu) and type 2 (anti-Ri or anti-Nova) were not detected.

Paraneoplastic neurological syndromes may present in many ways. Careful evaluation for the presence of an occult malignancy is important when there are more distinctive syndromes, such as Eaton-Lambert syndrome and subacute cerebellar degeneration. The index of suspicion of an occult malignancy should also be high in patients who present with opsoclonus.

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### Female predominance in spasmodic dysphonia

We were interested to see the sex prevalence results in the recent review of focal dystonia by Soland *et al.*<sup>1</sup> They found that of 956 patients with dystonia, 558 (58.4%) were female, for a ratio of 1.4:1. All but the cases of writer's cramp had more females than males. In their spasmodic dysphonia group the ratio was 2.6:1 female:male (n=36).

We have reviewed our database of the cases of spasmodic dysphonia seen at the Mayo Clinic, Scottsdale, between 1989 and 1996. There have been a total of 270 patients seen, 241 with adductor, and 29 with abductor spasmodic dysphonia. The overall ratio of females:males was 214:56 or 3.8:1. Thus females made up 79.3% of our population with spasmodic dysphonia. Broken down into subgroups, the female:male ratio was 4.1:1 for the adductors and 2.2:1 for the abductors. The mean age was 60 years for the men and 64.6 years for the women. Most (186) of these patients continue to be followed up for botulinum toxin injections.

Our results, in this much larger population of patients with spasmodic dysphonia, suggest a greater female predominance than most previous studies. The only other large magnitude study was by Blitzer and Brin<sup>2</sup> who reported 260 patients with idiopathic spasmodic dysphonia with a female:male ratio of 1.4:1. They later separated out their patients with abductor spasmodic dysphonia (n=32) and found a female:male ratio of 0.5:1. The other studies have been smaller, 21 and 41 patients, with a female:male ratio of 2.85:1<sup>3</sup> and 3.5:1.<sup>4</sup> Ludlow *et al.*<sup>5</sup> had only 16 patients and all but one were females. Given the overall similarities (female predominance) among the published series, we do not think that the female predominance is due to ascertainment bias. Whether there are genetic, hormonal, or autoimmune factors causing this is unknown. Only one series of abductor spasmodic dysphonia showed a male predominance, although our series had a female predominance. Certainly further investigation is needed.

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### Recurrent Guillain-Barré syndrome and CNS demyelination

It is commonly assumed that multiple sclerosis exclusively affects the central nervous system but there is growing evidence that it is not so. There is evidence that dysfunction and tissue damage in Guillain-Barré syndrome, chronic idiopathic demyelinating polyneuropathy, and multiple sclerosis result from immune reactions within the peripheral or central nervous systems.<sup>1</sup> Although it is commonly assumed that multiple sclerosis exclusively affects the central nervous system, central nervous system demyelination has been suggested in chronic idiopathic demyelinating polyneuropathy.<sup>2</sup> There are few reports of acute inflammatory demyelinating neuropathy associated with multiple sclerosis.<sup>3,4</sup>

Here, we report a patient with a recurrent Guillain-Barré syndrome who developed a first episode of central nervous system demyelination several years later.

A 26 year old woman was admitted to our hospital because of an acute right hemiparesis. In 1977, at the age of seven, the patient gradually developed a tetraparesis with areflexia. The neurological deficit reached a peak two weeks after the onset of symptoms. Her CSF showed 217 mg/dl protein without cells. The motor and sensory nerve conduction study included median, ulnar, peroneal, and sural nerves. The motor nerve conduction velocities (NCVs) and distal motor latencies were 46 ms and 5 ms respectively in the median nerve, 50 ms and 4 ms in the ulnar nerve, 39 ms and 7 ms in the peroneal nerve. Sensory nerve conduction and EMG studies did not disclose abnormalities. She slowly improved and was discharged three weeks later without symptoms. The patient was asymptomatic until 1991, when she was readmitted because of an ascending weakness and distal paraesthesiae, two weeks after a flu syndrome with fever. Neurological examination disclosed paresis in all four limbs, more severe distally in the upper limbs and proximally in the lower limbs. She was areflexic. Sensory examination showed a mild deficit to pin prick, and vibration and reduced proprioception was found distally in her four limbs. Lassegue sign was positive in both legs. The CSF contained 148 mg/dl protein and two leucocytes/mm<sup>3</sup>. Nerve conduction studies disclosed an absence of F responses and dispersion of motor nerve compound action potentials. Median, radial, ulnar, peroneal, and sural nerves were examined. Motor and sensory NCVs were normal except in the peroneal nerve (40 ms) and median nerve (48 ms). Distal motor latencies were 5 ms, 4 ms, and 8 ms in median, ulnar, and peroneal nerves respectively. The neurological deficit reached a peak three weeks after onset and she had recovered fully

in two months and was thereafter asymptomatic. A control electrophysiological study was performed several months later and no abnormalities were found.

In 1996, she was readmitted because of an acute right hemiparesis. Neurological examination showed a right pyramidal weakness, with right Babinski's sign and without sensory impairment. The haematological and blood chemical values were normal. A CSF analysis showed 24 mg/dl protein with three leucocytes/mm<sup>3</sup> and oligoclonal bands were detected. Brain MRI showed multiple T2 weighted hyperintense white matter lesions in both cerebral hemispheres, brain stem, and cerebellum. One of the lesions located in the left corona radiata displayed enhancement after gadolinium administration. High dose intravenous steroids were started and there was a pronounced clinical improvement. When the patient was discharged 10 days later the neurological examination was normal. Motor NCVs were greater than 50 ms in the arms and 45 ms in the legs, and no prolonged distal motor latencies were found. Transcranial magnetic stimulation showed a delay in central motor conduction in the right arm. An EMG examination did not show abnormalities. A new MRI performed two weeks later showed a decrease in inflammatory activity.

Our patient had a recurrent Guillain-Barré syndrome with subsequent development of a first attack of a central nervous system inflammatory demyelinating disease. Recurrent Guillain-Barré syndrome consists of multiple episodes of typical acute Guillain-Barré syndrome with CSF findings and EMG abnormalities during each individual episode similar to those described in the acute monophasic disease.<sup>5</sup> Although our patient does not fulfil criteria of clinically definite multiple sclerosis, MRI and CSF findings make the diagnosis very probable. Cranial MRI lesions have been found in chronic inflammatory demyelinating polyneuropathy although without clinical symptoms suggestive of multiple sclerosis.<sup>2</sup> Acute inflammatory demyelinating neuropathy associated with multiple sclerosis has not been described very often.<sup>3,4</sup> As far as we know, this is the first case of recurrent Guillain-Barré syndrome associated with a central nervous system demyelinating disease. In our patient both peripheral and central nervous myelin involvement were clinically symptomatic.

It seems that dysfunction and tissue damage in Guillain-Barré syndrome and multiple sclerosis result from impairment of immune regulation within the peripheral or central nervous system. Peripheral and central nervous system myelins exhibit a similar macromolecular organisation and some protein molecules are present in myelin from both systems; thus it is likely that, under certain circumstances, immune processes may be directed selectively against either peripheral nerves or CNS white matter. In the animal model, experimental allergic encephalomyelitis, the induction of the disease is accompanied by different degrees of peripheral involvement. Because closely related epitopes may be expressed in peripheral and central myelin, it is not unexpected that in some people there may be cross reactivity between peripheral and central nerve white matter.<sup>6</sup> On the other hand, it has been suggested that activated T lymphocytes may function as effector cells that exert cytotoxic activity towards Schwann cells or myelin.<sup>1</sup>

Although caution is appropriate in interpreting the few reports in the literature supporting the idea that peripheral nerves are involved in multiple sclerosis, it seems likely that at least in some patients both peripheral and central nerve myelin may be involved in an acute demyelinating attack. Perhaps the peripheral and central nervous systems share antigenic properties.

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## CORRESPONDENCE

### Non- or pseudoepileptic seizures?

We agree with Scull that consensus is badly needed for the nomenclature of manifestations which mimic, but are not, epileptic seizures.<sup>1</sup> His plea for using the term "non-epileptic seizure", however, is unconvincing. Non-epileptic seizures cover a wide range of diagnoses, both organic and psychogenic.<sup>2</sup> It is evident that, after it has been proved that seizures are not epileptic, another diagnosis should be sought. From the point of view of the epileptologist this diagnosis is, by definition, "non-epileptic", just as epileptic seizures may be called "non-syncope", "non-narcoleptic" or "non-dissociative" by other specialists. We think that Scull does not have this wide range in mind when he proposes to use the term "non-epileptic seizure".

From experience, we all know that there remains a group of patients, often with a diagnosis of epilepsy, who have non-epileptic seizures that closely mimic epileptic seizures and are referred to epileptologists. These seizures often turn out to be of psychogenic origin.<sup>3</sup> Harm can be done when this is not recognised—for example, when treatment consists of increasing doses of antiepileptic drugs. Why not name these seizures what they are—namely, "pseudoepileptic"? The prefix pseudo indicates that things are not what they seem to be. It does not imply that the seizures themselves are not a

real experience, or something to be ashamed of. It is our experience that this can be satisfactorily explained to patients. Therefore we prefer the use of "pseudoepileptic" instead of "non-epileptic seizures".

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### Scull replies:

I thank Kuyk and Leijten for their comments. In common English usage "pseudo" is a derogatory term and is taken by some patients to mean that the doctor thinks that their condition is fictitious. Dealing with the anger that patients feel when their diagnosis changes from "epilepsy" to a psychiatric label is always likely to be difficult. "Non-epileptic seizures" may not be an ideal label but aggravating patients with a term that can be misinterpreted is unhelpful.

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## PROCEEDINGS

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## NEUROFILAMENT GENE MUTATIONS AND AMYOTROPHIC LATERAL SCLEROSIS

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**Background and aims**—Amyotrophic lateral sclerosis (ALS) is a progressive neurodegeneration of the motor system with death usually occurring from respiratory failure within 3-5 years of diagnosis. Pathologically neurofilament accumulations are seen in the proximal axon and cell body. Whereas superoxide dismutase (SOD1) mutations have been implicated in 1%-2% of all cases to date, only five patients with neurofilament mutations have been described, all deletions in the heavy neurofilament subunit (NFH) tail. Therefore the NFH tail for mutations in the sporadic ALS population was analysed.

**Methods**—Clinical data and DNA were collected on patients attending a specialist clinic. Genotyping and mutation detection were performed by polymerase chain reaction (PCR) and single strand conformation polymorphism analysis (SSCP) followed by silver staining according to standard protocols. Samples showing band shifts on SSCP were subcloned and sequenced.

**Results and discussion**—Two novel mutations in a hypervariable region of the heavy neurofilament subunit gene (NFH) were found in two of 196 patients and none of 188 controls. The mutations are an 18 bp deletion and 24bp deletion from 1965-1988 and 1989-2006 respectively using the numbering of the published sequence. Each results in the loss of a single consensus phosphorylation motif, KSPXK. The clinical features of both patients were entirely typical of ALS. Both had El Escorial probable or definite ALS with onset in the limbs. The onset was at 66 and 73 years with survival of 19 and 33 months respectively.

**Conclusion**—Heavy neurofilament subunit gene mutations account for 1% of apparently sporadic ALS and are indistinguishable clinically from other forms.

## INVESTIGATION OF THE POLYMORPHISMS IN THE ecNOS GENE IN PATIENTS WITH AND WITHOUT DIABETIC PERIPHERAL NEUROPATHY

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Nerve ischaemia plays a central part in the pathogenesis of diabetic neuropathy (DN). The constitutive isoform of nitric oxide synthase (ecNOS) generates nitric oxide (NO) which modulates basal vascular tone and regulates nerve blood flow and may be a potential contributor to the pathogenesis of DN. We studied the distribution of the polymorphisms at 5' end of the ecNOS gene, the 27 bp repeat in intron 4 (ecNOS 4a/b) in 129 normal control subjects, 46 (21m) insulin

dependent diabetic patients without complications, 37 (19m) DN patients and 33 (15m) IDDM patients with retinopathy nephropathy with a mean age of onset of diabetes of 16.9, 19.7, and 16 years (range 1-40) respectively and mean duration of diabetes of 24.7, 25.4, and 27.7 (range 11-47) years respectively.

There was an excess of ecNOS 4b/a heterozygotes among those patients with DN and other microvascular complications (C2=5.45,  $P \leq 0.025$ , C2=4,  $P \leq 0.05$ ) respectively; also there was an excess of ecNOS 4b/a heterozygotes in DN patients with autonomic dysfunction in comparison to those without autonomic disturbances (C2=4.5,  $P \leq 0.05$ ). There were no significant differences in ecNOS genotypes between patients and controls.

In conclusion these data suggest that the ecNOS gene may be implicated in the pathogenesis of diabetic peripheral neuropathy.

## LYME NEUROBORRELIOSIS IN SOMERSET, ENGLAND

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Few publications concerning Lyme neuroborreliosis have appeared from the United Kingdom. Six cases seen in Somerset, England are reported here.

Three men and three women between the ages of 29 and 65 who had neuroborreliosis were seen in Somerset over three years. Three had history of rash (erythema chronica migrans) and two had symptoms of radiculitis. Among the five patients seen with cranial nerve lesions, facial palsy was the commonest. One had peripheral neuropathy only. Spontaneous resolution of initial symptoms and signs as the condition progressed was a feature of acute cases. Pleocytosis with raised protein in the CSF was seen in all patients except one who already had treatment with penicillin. Lyme serology was positive in CSF and blood in all cases.

It is suggested that fleeting symptoms and signs are good pointers to the diagnosis of Lyme neuroborreliosis. Abnormality of CSF in untreated cases, especially Lyme serology, is essential.

## NEUROLOGICAL DEGENERATION IN THE WOLFRAM (DIDMOAD) SYNDROME

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Forty five patients with this rare autosomal recessive syndrome were ascertained from multiple sources throughout the United Kingdom. The ascertainment criterion was childhood onset of diabetes mellitus and optic atrophy. The patients were aged 5-47 years with a mean of 29.5 years. Most patients also had diabetes insipidus and deaf-

ness, in accord with the recognised features of this syndrome. However, a new finding was the frequency of neurological complications which occurred in 20% of those under 20 and in 78% of those over 20. Ataxia was the most common symptom; others included startle myoclonus and central apnoea. Four of 12 deaths were due to central respiratory failure. MRI (n=7) disclosed cerebellar and brain stem atrophy, loss of pituitary bright signal and thinned optic nerves. Muscle biopsies (n=9) showed normal respiratory chain function and analysis of lymphocytic mitochondrial DNA showed no rearrangements (n=32). The clinical and neuroradiological findings indicate that cerebellar and brain stem degeneration are significant and common complications in older patients with the Wolfram syndrome.

## VISUAL INVERSION OR ROTATION ASSOCIATED WITH DIFFERENT TYPES OF CEREBELLAR INFARCTION

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Inversion, rotation, or "tilting" of vision is an unusual phenomenon. The pathophysiological mechanisms and anatomical structures involved are not well understood. Five patients are described in whom a history of acute visual inversion or rotation was elicited, associated with vertigo and in some with additional symptoms. In each case this was transient and in one there were a number of episodes. The visual disturbance was not always recorded in the initial history. Each patient underwent CT and/or MRI imaging of the brain. Four patients had unilateral infarction in the territory of the posterior inferior cerebellar artery (PICA). The fifth had bilateral infarctions in superior cerebellar artery (SCA) territories. Visual inversion has been reported hitherto as a rare symptom in association with vertebral basilar ischaemia and Wallenberg's syndrome. More recently there have been a few reports demonstrating cerebellar infarction, most involving the PICA territory, in particular that of its medial branch. Infarction of other areas of the cerebellum can be involved. Possible mechanisms for this phenomenon were discussed. On direct questioning this symptom was more common in cerebellar infarction than previously thought.

## INTEGRINS AND OLIGODENDROCYTE DIFFERENTIATION

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**Aims**—Normal myelination of the CNS during development is obtained by the differentiation of migratory precursor cells into mature postmitotic oligodendrocytes. The aim of this study was to examine the role of

the integrin family of cell surface receptors for extracellular matrix (ECM) in this differentiation process.

**Methods**—In vitro methods, involving purified rodent oligodendrocyte precursors, purified ECM ligands, and blocking antibodies and peptides were used.

**Results**—Integrin expression can reflect the state of cellular differentiation. Oligodendrocytes maintain an immature pattern of integrin expression in the presence of BFGF, a growth factor which is known to inhibit differentiation in terms of myelin protein expression.

Integrin expression can affect the state of cellular differentiation. After the withdrawal of BFGF normal maturation is disrupted by specific blockade of b1 integrins; the cells show a reduced ability to complete the normal maturation that follows growth factor withdrawal and show an increased degree of apoptosis. This finding is paralleled by the finding that morphological maturation is optimal on a substrate of merosin, a ligand for the a6b1 integrin. It is suggested that an extracellular signal, mediated by a b1 integrin, is necessary for oligodendrocyte precursors to complete successfully the normal maturational process.

**Discussion**—In rodent cells in vitro, the extracellular environment may influence oligodendrocyte differentiation via their integrin cell surface receptors. Evidence from others suggests that a similar situation may hold in humans: thus those with merosin negative congenital muscular dystrophy have been reported to show white matter abnormalities on MRI. It is suggested that integrin mediated cell-ECM interactions may be critical for the development and maintenance of normal myelination in vivo. Further understanding of oligodendrocyte biology, including the behavioural effects of cell-ECM interactions, will be crucial in the design of strategies for enhancing repair in patients of all ages with acquired demyelinating nervous system damage.

#### USE OF SUBCUTANEOUS APOMORPHINE FOR TREATMENT OF NOCTURNAL DISABILITIES AND OTHER SPECIFIC SYMPTOMS IN PARKINSON'S DISEASE

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**Aims**—The efficacy of apomorphine in the treatment of specific symptoms in Parkinson's disease (PD) was investigated, in particular nocturnal disabilities and restless legs syndrome (RLS), refractory to oral therapy.

**Methods**—Six patients are described with disabling nocturnal symptoms such as fragmented sleep, pain, nocturia, hallucinations, and morning akinesia and two with RLS refractory to long acting levodopa. Apomorphine was administered overnight (continuous infusion using Graseby pump) from 8 00 pm to 8 00 am (mean dose 60 mg, range 30-84 mg). A nocturnal diary was kept by nursing staff and, in two patients, placebo (saline) infusion was administered in a double blind fashion. Further specific uses of apomorphine are described.

**Results**—After apomorphine but not placebo, there was abolition of nocturnal freezing, nocturia and fragmented sleep. Mean off periods fell from five hours to one hour. In the two patients with RLS, there was complete relief of symptoms and the pain

score fell from 7 to 2 (scale 0-10). Apomorphine was also used for (a) lower extremity parkinsonism: one patient with severe freezing and falls, wheelchair bound in spite of oral therapy, is now ambulant with apomorphine; (b) off period pain: four patients with severe off period pain and paraesthesia (shoulder (two) and leg (two)) use penject apomorphine without any neuropsychiatric complications. One remains on apomorphine only; (d) malignant parkinsonism and neuroleptic malignant syndrome (NMS): one patient with severe PD in a rigid akinetic mute state after an infection and one with NMS have responded well to subcutaneous high dose apomorphine.

**Discussion**—Subcutaneous apomorphine is highly effective for treating specific disabling refractory nocturnal symptoms and other atypical symptoms of PD. Furthermore, apomorphine seems to be highly effective for treatment of RLS and off period pain when conventional therapy is ineffective.

#### ATYPICAL PARKINSONISM IN THE AFROCARIBBEAN POPULATION IN THE UK

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**Aims**—Parkinson's disease (PD) is thought to occur less often in African populations. The incidence of PD in the migrant AfroCaribbean population in the United Kingdom is unknown. In this study the pattern of parkinsonism in this group living in London has been investigated.

**Methods**—The consecutive case files of over 150 patients attending movement disorders clinics in two areas of London with a high AfroCaribbean population, discharge summaries from medical wards and general practitioner (in the catchment area) records are being reviewed. In addition, door to door knocking assessment for Parkinsonism was carried out in one electoral ward.

**Results**—So far 18 cases of Parkinsonism have been identified in patients of AfroCaribbean origin. Fourteen out of 18 cases (83.3%) show non-familial atypical levodopa unresponsive parkinsonism. One patient has positive spinocerebellar atrophy (type 3) mutation. Screening for Wilson's disease in appropriate patients and dentate rubropallid Luysian atrophy in 2 has been negative. High field brain MRI and brain CT have been unremarkable and magnetic resonance spectroscopy, performed in two cases, has shown severe bilateral symmetric reduction in striatal N-acetyl aspartate:creatine ratios.

**Discussion**—This ongoing study has shown that parkinsonism is probably more common than realised in AfroCaribbean subjects and these patients may be more susceptible to atypical parkinsonism. The reason for this is unclear and may reflect genetic or environmental factors. Further epidemiological studies considering this issue are required.

#### ORTHOSTATIC HYPOTENSION DUE TO SELEGILINE IN PATIENTS WITH PARKINSON'S DISEASE: POSSIBLE MECHANISMS AND CLINICAL RELEVANCE

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Selegiline was initially reported by the Deprenyl and Topopherol Antioxidative Therapy of Parkinsonism (DATATOP) Study to delay the need for levodopa in Parkinson's disease (PD). However, the United Kingdom

PD Research Group (UKPDRG) trial and longer follow up in the DATATOP study failed to show a neuroprotective effect. Selegiline combined with levodopa was associated with greater all cause mortality than levodopa alone in the UKPDRG trial, although no causal relationship with selegiline was proved. Mortality data from the UKPDRG trial is currently being analysed in a cause of death (CODE) study. Recently, it was found that long term selegiline therapy caused selective and often severe orthostatic hypotension on head up tilt which was reversed by drug withdrawal. This finding was confirmed in a second study which examined the effects of head up tilt and standing on blood pressure, heart rate, and plasma catecholamines in 20 PD patients taking selegiline. Patients were examined on selegiline (10 mg/day) after two weeks on 5 mg/day, and at 4, 7, and 21 days after cessation. Selegiline was associated with systolic hypotension on head up tilt and standing as well as a supine pressor effect. The orthostatic hypotension reversed within seven days of drug cessation. The combination of orthostatic hypotension and a supine pressor effect is similar to the cardiovascular actions of selegiline's major metabolites, amphetamine and met-amphetamine, at doses which cause psychic symptoms in normal humans, although non-selective blockade of monoamine oxidase was not excluded. Quantification, currently under way, of plasma amphetamine, metamphetamine, tyramine and *p*-hydroxynorepinephrine concentrations may further define the mechanism of selegiline's cardiovascular actions.

#### ROLE OF PROLONGED HEAD UP TILT AND URINARY SODIUM EXCRETION IN SYNCOPE

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**Aim**—To evaluate the role of prolonged head up tilt (HUT) and 24 hour urinary sodium excretion (USE) as a first line investigation in recurrent syncope. Recurrent unexplained syncope occurs in up to 30%-50% of cases and low sodium excretion or cardiac arrhythmias have been implicated. A further explanation is the occurrence of the postural orthostatic tachycardia syndrome (POT).

**Methods**—30 subjects referred for investigation of blackouts (15 men, 15 women, mean age 46 years, range 16-70) and 15 controls (10 men, five women, mean age 40 years, range 20-60) were studied using cardiovascular autonomic function tests, ECG, EEG, prolonged (30 min) HUT (60°), blood biochemistry, and 24 hour USE.

**Results**—22 out of 30 subjects (but not controls) had a positive tilt test defined by presyncopal symptoms on HUT. Blood pressure and heart rate (BP, HR) fell in two subjects who had cardiac arrhythmia on subsequent 24 hour Holter monitoring. Mean BP fell with rise in HR >120 beats per minute in three subjects (POT type 2) whereas mean BP was unaffected in others despite symptoms and rise in HR (<120 bpm) (POT, type 1). Routine blood biochemistry and haemoglobin were normal in all and 24 hour USE was low normal (mean 137 mmol, range 100-500, n = 13). Five subjects had low USE and salt supplementation (120 mmol/day) abolished syncope. EEG was abnormal in one who was negative to HUT.

**Discussion**—(1) Inexpensive prolonged (30 min) HUT and 24 hour USE could be incorporated as a first line test for investigation of

syncope and helps in identifying cardiac syncope and POT (2) Those with low 24 hour USE may benefit from salt supplementation (3) Further investigations (EEG, Holter monitoring) are indicated in elderly patients, those with negative HUT or positive HUT with hypotension and bradycardia.

SHIFT FROM Th1 TO Th2 LYMPHOCYTE PHENOTYPE INDUCED BY MONOCLONAL ANTIBODY TREATMENT OF MULTIPLE SCLEROSIS PATIENTS  
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In an attempt to suppress the autoimmune inflammation of multiple sclerosis, 16 patients were treated with the humanised monoclonal antibodies Campath-1H and anti-CD4. Changes in immunological activity were monitored over time by measuring the cytokines secreted in vitro by each patient's peripheral blood mononuclear cells when stimulated with phytohaemagglutinin. Comparison of the relative IFN $\gamma$  and IL-4 secreted per T cell showed a shift from a predominantly Th1 to a Th2 response. This shift had partially reversed by 12 months after treatment. These changes paralleled the clinical response with clinical disease suppression induced for 12 months on average. This response is currently being compared to in vitro lymphocyte depletion by magnetic bead or FACS separation.

This study has demonstrated that monoclonal antibody treatment may modulate the inflammatory activity of multiple sclerosis with beneficial clinical consequences, which are reflected by changes in T lymphocyte phenotype.

MELAS OR MNGIE?: AN UNUSUAL PRESENTATION OF A MITOCHONDRIAL RESPIRATORY CHAIN DISORDER  
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An 18 year old woman presented in 1996 with status epilepticus; two years previously she had undergone a partial gastrectomy and Roux-en-Y formation for repeated episodes of pseudo-obstruction for which no cause was identified. On admission, she had a lactic acidosis. Subsequent investigations showed 10% ragged red fibres on muscle biopsy, and a 3243 mutation on mitochondrial DNA analysis in blood and muscle. She has since had two further admissions with status, both preceded by a migraine headache, and has developed deafness. Her last admission was complicated by recurrent anorexia and vomiting which eventually settled.

Although our patient had the 3243 mutation usually associated with MELAS, she is phenotypically quite unlike this syndrome; unusual presentations of 3243/MELAS are recognised, but gastrointestinal dysmotility has not been described. Gastrointestinal dysmotility does occur in mitochondrial respiratory chain disease as the MNGIE syndrome (mitochondrial neurogastrointestinal encephalomyopathy). However, these patients commonly have ophthalmoplegia and peripheral neuropathy which our patient does not, and epilepsy and migraine are not described, which are prominent features in this case.

This case emphasises two points; firstly, that patients with mitochondrial disease may initially present to specialists other than neurologists and the diagnosis may be delayed.

Secondly, that whereas certain clearly identifiable phenotypic mitochondrial diseases exist, some patients do not fit easily into such categories.

DOES AXONAL LOSS AND DEMYELINATION OCCUR TOGETHER IN THE SAME LESIONS IN MULTIPLE SCLEROSIS?

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It has been proposed that magnetisation transfer (MT) provides information about the integrity of myelin. Similarly, the measurement of N-acetyl aspartate (NAA)—an amino acid localised to neurons and their processes—by magnetic resonance spectroscopy (MRS) has been used as an index of axonal loss and/or dysfunction in multiple sclerosis (MS).

MRI, MT imaging, and MRS were carried out on 18 patients with clinically definite MS. The group comprised patients with a wide range of disability (range 2-25 years, median 7 years). Single voxel MRS localised to a chronic area of high signal from hemispheric white matter which had been present for greater than 12 months was collected. MR was then calculated from the corresponding volume.

NAA was quantitated using the fully relaxed water signal as an internal standard of reference.

There was a significant correlation between a reduction in the absolute concentration of NAA from a chronic MS lesion (range 3.5 mM-12.8 mM, median 9.25mM) visible on MRI and reduction in the MT value (range 14.6-28.6, median 25.3) from the same lesion ( $P < 0.002$ ,  $r = 0.71$ ).

These preliminary results support the hypothesis that demyelination and axonal loss occur together in destructive MS lesions and that there may be a common pathological mechanism producing both.

MOLECULAR GENETIC DIAGNOSIS OF FREIDREICH'S ATAXIA IN A PEDIGREE WITH APPARENT AUTOSOMAL DOMINANT SPINOCEREBELLAR DEGENERATION

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Freidreich's ataxia (FRDA) is an autosomal recessively inherited disorder in which spinocerebellar degeneration occurs, usually from the second decade of life. Recently, FRDA has been linked with mutations (GAA triplet repeats or point mutations) of the intronic X25 gene on 9q13. Genome analysis of affected members of a pedigree with presumed adult onset, autosomal dominant spinocerebellar degeneration has yielded an unexpected diagnosis of FRDA.

A 26 year old man was seen with a seven year history of progressive dysarthria and limb ataxia. Examination also disclosed pes cavus, nystagmus, hyperactive lower limb reflexes and intact joint position sense. His 22 year old sister has had poor balance for seven years, and is now wheelchair bound and dysarthric. Their 46 year old father (who misuses alcohol) has had ataxia for at least two years. The daughter of the proband has presented with transient incoordination at the age of 18 months. PCR using primers for the GAA repeat at 9q13-21.1 on the proband and his sister has disclosed expanded allele smears of

between 2000 and 3000 bp, making FRDA highly likely.

Symptoms and signs of ataxia in the proband's father and daughter implied a dominant mode of inheritance. It is conceivable that FRDA heterozygotes can develop ataxia, particularly in association with environmental insults.

STROKE TRIALS: DO STROKE PATIENTS PREFER DEATH OR DISABILITY?  
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*Background*—Some treatments for acute stroke—for example, thrombolysis, may increase the risk of death, but also reduce the proportion of dependent survivors. Therefore, groups of independent and dependent stroke survivors were compared as to how they rated their own quality of life.

*Methods*—The EuroQol is a generic instrument for the measurement of health related quality of life (HRQoL). It includes a visual analogue scale on which patients rate their own health between 0 and 100 (worst and best possible), so providing an overall numerical estimate of their HRQoL. HRQoL was assessed by postal follow up with the EuroQol questionnaire in 1125 United Kingdom patients randomly selected from patients enrolled in the International Stroke Trial.

*Results*—905 patients responded (response rate 80%). Mean overall HRQOL among independent patients was 68 (95% CI 23 - 100). This was significantly greater than in patients who were dependent at follow up (mean = 44, 95% CI 1 - 87;  $P < 0.01$ ). However, 83% of dependent stroke survivors reported overall HRQOL within the range of the independent survivors (23 to 100) and 15% rated their overall HRQOL as greater than 68 (the mean of the independent survivors).

*Discussion*—A high proportion of survivors of stroke who are dependent in ADL rate their HRQOL surprisingly highly, sometimes as high as independent survivors. Stroke free patients may prefer death to dependent survival, but patients who have survived a stroke in a dependent state seem to view things differently.

SUPRATENTORIAL WHITE MATTER VOLUMES ON MAGNETIC RESONANCE IMAGES CORRELATE WITH COGNITIVE PERFORMANCE IN MULTIPLE SCLEROSIS (MS)  
S G M Edwards, N Roberts, L D Blumhardt, University of Nottingham, Nottingham, UK.

Despite the high sensitivity of MRI and the high prevalence of cognitive deficits in MS, correlations between neuropsychological test performance and various MRI parameters have been weak and inconsistent. In the present study the aim was to correlate neuropsychological indices with the volumes of supratentorial structures and the area of the corpus callosum in 40 patients with clinically definite MS, using 3D acquired MPRAGE (Magnetisation Prepared Rapid Acquisition Gradient Echo) and stereology. All subjects underwent a neuropsychological battery, including tests of intellect, memory, recognition, attention, visuospatial skills, and frontal executive functions. A global cognitive index (GCI) was derived from the test scores.

Supratentorial white matter (SWM), grey matter, and ventricles comprised 22.2

(2.7)%, 32.4 (3.6)%, and 0.93% (0.6)%, respectively, of total cranial volume, and corpus callosum 2.9% (0.6)% of mid-sagittal area. SWM correlated with GCI ( $\rho = -0.63$ ,  $P < 0.0001$ ) and with many individual cognitive tests, including IQ loss (premorbid IQ—estimated IQ) ( $\rho = -0.44$ ,  $P = 0.007$ ). GCI was also correlated with corpus callosal area ( $\rho = -0.49$ ,  $P < 0.002$ ). Percentage grey matter was not significantly correlated. These volume/function relations presumably reflect the effects of subcortical myelin and axonal loss on the widely distributed neural networks that subserve different cognitive tasks. If serial MRI volume estimations can index accumulating cognitive deficits, this technique may be useful in therapeutic trials.

LOW GRADE LEAKAGE ACROSS THE BLOOD-BRAIN BARRIER IN WHITE MATTER CORRELATES WITH DISABILITY IN MULTIPLE SCLEROSIS

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The aim was to investigate the extent of blood-brain barrier damage in normal appearing white matter (NAWM) as a possible index of disease severity. We analysed the pre and post-Gd-DPTA T1 weighted signal intensities from NAWM on MRI in 18 patients with relapsing and remitting MS (RRMS) and 14 with secondary progressive MS (SPMS), to obtain a white matter enhancement index (WMEI), such that:

$$\text{WMEI} = \frac{\text{Post-Gd-DPTA T1 value} - \text{Pre-Gd-DPTA T1 value} \times 100}{\text{Pre-Gd-DPTA T1 value}}$$

Overall, WMEI was significantly correlated with disability (expanded disability status scale,  $\rho = 0.62$ ,  $P = 0.0002$ ); scripps neurological rating scale,  $\rho = -0.66$ ,  $P < 0.0001$ ; ambulation index,  $\rho = 0.54$ ,  $P = 0.0015$ ), with stereologically acquired volume estimates of cerebral white matter ( $\rho = 0.45$ ,  $P = 0.01$ ); cerebellum  $\rho = -0.47$ ,  $P = 0.0085$ ) and with disease duration ( $\rho = 0.4$ ,  $P = 0.023$ ). The relation with age was weak ( $\rho = 0.35$ ,  $P = 0.05$ ). Mean WMEI was significantly higher in SPMS (9.2 (3.8)) than in RRMS (5.2 (2.0)) ( $P = 0.0002$ ).

The existence of a subtle blood-brain barrier defect which is significantly associated with white matter volume and disability and more pronounced in progressive disease, suggests a possible causal relation with axon and/or myelin loss. WMEI may be a more reliable MRI index of fixed neurological deficit than visible lesion loads on T2 weighted or Gd-DPTA enhanced images.

FLAIL ARM SYNDROME IN MOTOR NEURON DISEASE

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**Aims**—The flail arm syndrome is defined as predominately bilateral lower motor neuron involvement of the upper limbs with no significant functional involvement of other regions. The objective was to determine whether this syndrome represents a clinical subtype of motor neuron disease with a more favourable prognosis.

**Methods**—Details of 440 patients referred to a specialist motor neuron disease (MND) clinic between January 1990 and September 1996 were taken retrospectively from the

clinical notes and entered into a database. Subjects with flail arm syndrome were identified and compared with the rest of the MND population.

**Results**—The median follow up period has been 16.5 months (95% CI, 14.4–18.6 months). Thirty nine patients out of a total of 440 were identified with the flail arm syndrome. The male:female ratio was 9:1 in the flail arm group and 1.5:1 in the MND group ( $P = 0.0015$ ). The median survival from symptom onset in the flail arm group was 58.4 months (95% CI, 46.9–70.0 months) compared with 40.7 months in the MND group (95% CI 34.4–47.0 months,  $P = 0.199$ ). The flail arm syndrome was not identified as an independent factor determining survival, implying that the improved survival relates to an association with other good prognostic factors such as limb rather than bulbar onset and favourable El Escorial category.

**Discussion**—The flail arm syndrome represents a subtype of MND, occurring predominantly in males. It is probably associated with a more favourable prognosis, despite early involvement of cervical anterior horn cells.

NEUROIMAGING AND NARCOLEPSY: ACTION OF MODAFINIL

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**Background**—There are about 20 000 subjects with the narcoleptic syndrome in the United Kingdom. Diagnosis depends on the definite presence of cataplexy defined as laughter triggered loss of motor tone with mutism and dysarthria accompanied by facial muscle flickering. Additional features are excessive daytime sleepiness, presleep dream timing, interrupted night sleep, and a high frequency of sleep paralysis and other motor parasomnias. Present treatment is unsatisfactory. The development of the sleep preventing drug modafinil may allow more effective treatment. The mode of action of this drug is not known.

**Methods**—Twelve subjects with the narcoleptic syndrome and 12 controls were studied using functional MRI of auditory and visual cortical areas, recording evoked responses to periodic auditory and visual stimuli. Echoplanar MR images were acquired using a 1.5 Tesla GE Signa. The action of modafinil (400 mg) as a single oral dose (16 subjects) was compared with placebo (eight subjects).

**Results**—Modafinil caused an increase in self rated levels of alertness in seven of eight narcoleptic subjects. Calcarine and auditory cortical activation, as determined by pixel count, was higher in normal than narcoleptic subjects and in males than females. There was no significant difference in pre and post-modafinil activation levels in either control or narcoleptic subjects. However the response to modafinil, but not placebo, was correlated with pretreatment level of activation (audi-

tory,  $r = 0.7$ ,  $P = 0.002$ ; visual,  $r = -0.8$ ,  $P = 0.001$ ).

**Conclusion**—Functional MRI shows a slightly lower mean cortical activation in narcoleptic than control subjects. Low activation levels are increased by modafinil.

PUTAMINAL METABOLITE CHANGES IN UNTREATED AND LEVODOPA TREATED IDIOPATHIC PARKINSON'S DISEASE

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**Aim**—To use magnetic resonance spectroscopy (MRS) centred on bilateral putamen and quantify putaminal neuronal and membrane dysfunction (measurement of N-acetyl aspartate:creatin+phosphocreatine (NAA:Cr+PCr) and choline (NAA:Cho) ratios in untreated, levodopa treated dyskinetic idiopathic Parkinson's disease and controls.

**Methods**—MRS was performed (1.5 Tesla GE Signa system, PRESS spectra, TR=2000 ms, TE=136ms, voxel size  $1.8 \times 0.2 \times 2 \text{ cm}^3$ ) centred on bilateral putamen of 9 untreated PD (mean age 60 (11) years, mean duration 1.5 years, mean Hoehn and Yahr 1.6), seven levodopa treated PD patients with dyskinesiae (57 (13) years, duration of PD 9.5 years, Hoehn and Yahr 3.6), and 11 healthy controls (age 53 (12) years). Ratios were calculated by a blinded observer using SAGE/IDL software.

**Results**—Mean NAA:Cho ratios from the putamen contralateral to the most affected side were highly significantly diminished in untreated PD compared with controls (0.97 (0.14) v 1.26 (0.28),  $P = 0.009$ ). This was not found in the levodopa treated group. NAA:Cho ratios from contralateral putamen were lower in untreated PD compared with treated PD ( $P = 0.06$ ). NAA:Cr+PCr ratios from the contralateral putamen were lower in untreated and treated PD compared with controls but this was not significant (1.22 (0.35), 1.26 (0.12), 1.4 (0.33) respectively). In untreated PD, NAA:Cr+PCr ratios were significantly lower in CL compared with ipsilateral putamen (1.10 (0.12) v 1.32 (0.22),  $P = 0.03$ ).

**Discussion**—In untreated PD, decreased putamen NAA:Cho ratios may reflect a functional abnormality due to striatal deafferentation. In levodopa treated PD, normal NAA:Cho ratios suggest that NAA:Cho ratios may be affected by levodopa therapy and further longitudinal studies are required.

AMNESIA FOR CHILDHOOD CORRELATES WITH NON-ORGANIC SYMPTOMS

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**Aim**—To investigate long term memory and depression, in patients with neurological disability or handicap, without impairment or pathology (non-organic neurology).

Amnesia for childhood correlates with non-organic symptoms

	Organic	Non-organic	Significance
n	55	45	
1mem (y; median)	4	3	NS
Cmem (y; median)	6	11	$P < 0.001$
Memory blanks (n)	3	18	$P < 0.001$
BASDEC score (median)	4.0	7.0	$P < 0.05$

**Method**—100 consecutive new neurological out patients were asked their age at first ever memory (Imem) and at onset of continuous memory (Cmem), and about memory blanks; evidence of depression was sought (brief assessment schedule depression cards: BASDEC. Score >6.5 suggests depression).

**Results**—The table presents the results.

**Conclusion**—“Non-organic” neurological presentation is commonly associated with a delayed onset of continuous memory.

PERSISTENCE OF MONOSYNAPTIC GROUP IA PROJECTIONS BETWEEN ANTAGONIST MUSCLES IN SUBJECTS WITH PERINATAL BRAIN DAMAGE  
M C O'Sullivan, S Miller, J A Eyre, Newcastle upon Tyne University, Newcastle upon Tyne, UK.

**Introduction**—Cocontraction of antagonist muscles is characteristic of spastic cerebral palsy but not of adult onset spasticity. Monosynaptic group IA projections from biceps brachii to motoneuronal pools throughout the brachial plexus are present at birth and become restricted during the first two years.

**Hypothesis**—these projections persist in children with spastic cerebral palsy, but not in adult onset spasticity.

**Subjects**—(1) Cross sectional study of 372 normal subjects (birth to 55 years), 38 subjects with spasticity of perinatal origin but differing cortical pathologies (16 Rett syndrome, 11 tetraparetics, 11 hemiplegics), and 11 adults with spasticity after stroke. (2) Longitudinal study (seven years) of 50 normal neonates, 30 neonates at high risk for cerebral palsy, 11 of whom subsequently developed spastic tetraparesis.

**Methods**—Brief mechanical taps were applied to the tendon of biceps brachii with responses recorded in the surface EMG of biceps, triceps, deltoid, and pectoralis major.

**Results**—Heteronymous excitatory reflex responses were frequent at birth and rapidly decreased in frequency by two years. A normal pattern of heteronymous reflexes was found in adults after stroke. In the cross sectional and longitudinal studies all subjects with spasticity from perinatal brain damage showed persistence of monosynaptic heteronymous excitatory responses to triceps, but normal restriction of reflexes to deltoid and pectoralis major.

LONG TERM EFFECTS OF NEUROREHABILITATION IN MULTIPLE SCLEROSIS (MS): A LONGITUDINAL STUDY  
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The long term effects of neurorehabilitation in MS have not been demonstrated, yet are crucial in determining the duration of benefit and frequency of review.

Fifty consecutive patients (mean age 45 years, 29 female) with progressive MS admitted for neurorehabilitation were assessed on admission (A), discharge (D), and then at three monthly intervals for one year (Y). The measures used were: Kurtzke's expanded disability status scale (EDSS) and functional systems (FS); functional independence measure (FIM); London handicap scale (LHS); and general health questionnaire (GHQ). Trends in performance levels were plotted.

Twelve month data were collected for 92% of patients. Over this period, neurological status declined (EDSS medians A=6.8,

D=6.8, 1Y=8.0), whereas disability (FIM medians A=61.5, D=74, 1 Y=63.5), handicap (LHS means A=60.3, D=64.4, 1 Y=61.6), and mood (GHQ medians A=9.5, D=1.5, 1Y=4) maintained some improvement. Although a gradual reduction in disability, handicap, and mood was recorded, average scores remained above admission level. This suggests that the benefits gained from neurorehabilitation are sustained, at least in part, over a 12 month period, despite deteriorating neurological status.

CATEGORY SPECIFIC SEMANTIC LOSS IN DEMENTIA OF ALZHEIMER'S TYPE: INSIGHTS INTO THE ORGANISATION OF KNOWLEDGE IN THE BRAIN  
P Garrard, K Patterson, P Watson, J R Hodges, University of Cambridge Neurology Unit, Cambridge, UK.

In the context of focal brain injury, selective loss of semantic knowledge of natural kinds or artefacts is usually considered to reflect the differential importance of temporal and frontoparietal regions to the representations of perceptual and functional attributes, respectively. It is harder to account for as a feature of a more diffuse process, and previous cross sectional analyses of DAT patients have differed over whether category effects occur. In a series of 58 patients with probable DAT there was a significant group advantage for artefacts, possible reasons for the inconsistency of this finding in other studies was explored. A multiple single case strategy disclosed patients with consistent advantages for both domains of knowledge. By ranking the group according to measures of naming performance and global intellectual ability, a strong double dissociation of semantic categories was shown, dependent on the former but not the latter variable. The longitudinal profiles of individual patients were also examined. The findings were discussed in the context of two competing theories of semantic breakdown in DAT: an anatomically based model, and a distributed model. It is concluded that the findings are in keeping with the predictions of the former.

INTRA AND INTEROBSERVER VARIABILITY IN THE ASSESSMENT OF TEMPORAL LOBE ATROPHY  
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**Introduction:** Quantification of the relative involvement of right and left temporal lobes in cases of semantic dementia is an essential first step in elucidating the contributions of these structures to the neural representation of semantic knowledge. Formal volumetric assessment is time consuming, and as yet neither a method nor a range of normality has been described. For within subject comparisons a semiquantitative assessment of the degree of atrophy is an acceptable alternative approach. An attempt was therefore made to validate this method.

**Methods**—Two senior neuroradiologists gave independent assessments of the degree of atrophy of both temporal lobes on coronal MRI images of 14 patients with the clinical syndrome of semantic dementia. Anterior and posterior slices were graded on an integer scale from 0 (normal) to 3 (severe atrophy). The procedure was repeated after 24 hours.

**Results**—The strength of within observer agreement ranged from moderate to very good (K 0.41-1.00), with the strongest

agreement on binary judgements (normal v abnormal - direction of asymmetry). Strength of between observer agreement was much weaker overall (K 0.16-0.62), with the strongest agreements again emerging for binary judgements.

**Conclusion**—Subjective assessment of temporal lobe atrophy is too variable a measure to justify its use in studies of functional-anatomical correlates of temporal lobe atrophy.

CORONARY ARTERY BYPASS SURGERY (CABS) AS A TEST BED FOR NEUROPROTECTION: A RANDOMISED TRIAL OF REMACEMIDE WITH NEUROPSYCHOLOGICAL DEFICIT AS THE END POINT AFTER CORONARY ARTERY SURGERY  
M J G Harrison, S P Newman, J Arrowsmith, J Stygall, N Timberlake, T Shah, W Pugsley, University College London Medical School and UCL Hospitals, London, UK.

Using cardiopulmonary bypass (CPB) as a human model of cerebral ischaemia the hypothesis that the glutamate antagonist remacemide hydrochloride (RH) might reduce both the incidence and severity of persistent cognitive deficits after coronary artery bypass surgery (CABS) was examined.

One hundred and seventy patients scheduled to have elective, primary CABS were randomly allocated to receive RH (600 mg) daily (n=87) or placebo (n=84) for five days before and five days after CABS. Cognitive function was assessed one week before and six days and eight weeks after CABS using a battery of 10 neuropsychological (NP) tests. An NP deficit was defined as a deterioration of more than one SD from the preoperative mean test score in two or more tests.

At six days 37% on placebo and 41% on treatment showed a deficit. By six weeks this had fallen to 12% on placebo and 9% on RH (Fisher's exact P = 0.6). The study showed no evidence of neuroprotection by this glutamate antagonist but the paradigm seems useful for screening such compounds.

MEASURING NEUROLOGY: IS BIGGER BETTER? COMPARATIVE MEASUREMENT PROPERTIES OF THE FUNCTIONAL INDEPENDENCE MEASURE (FIM) AND BARTHEL INDEX (BI)  
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New disability measurement instruments must demonstrate advantages over existing measures to warrant adoption into routine clinical practice, particularly when they are resource consuming. The widely used Barthel Index (BI) is generally viewed as too simplistic, crude, and unresponsive (insensitive to clinical change) to evaluate therapeutic effectiveness. The functional independence measure (FIM) was specifically developed to enable reliable, valid, and responsive disability measurement. Despite increasing worldwide use, and being widely regarded as a gold standard measure, evidence in support of the FIM's superiority is limited.

This multicentre study compares the reliability, validity, and responsiveness of the FIM and BI in 209 patients undergoing inpatient neurorehabilitation.

Internal consistency reliability (Cronbach's  $\alpha$ ) of both instruments was high; FIM=0.96; BI=0.91. Validity was compared by examining correlations between FIM and BI scores

with six other disability measures. Correlations were almost identical with all BI correlations within 1 SE of FIM correlations ( $<0.07$ ). Responsiveness was determined by calculating an effect size from admission and discharge ratings and was similar (FIM=0.52; BI=0.56).

Whereas reliability, validity, and responsiveness of both instruments is demonstrated the complex and costly FIM offers little over the simple and cheap BI in terms of measurement properties in this population.

#### FUNCTIONAL MAGNETIC RESONANCE IMAGING (FMRI) OF A SHORT TERM MEMORY TASK

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In this work FMRI is used to identify regions of the brain activated during separate parts of a short term memory task.

Whole brain images were obtained on a 3.0 T EPI scanner every two seconds. Four volunteers were studied. A four part short term memory task was used consisting of (1) Reception; viewing three numbers over three seconds. (2) Retention; remembering the numbers for 11 seconds. (3) Recall and match; matching a number with the first 3. (4) 12 seconds rest. 32 tasks were performed. Images taken during rest were compared with images taken during the first three parts of the task. Significant changes in pixel intensities between rest and task were detected using a *t* test showing a threshold at  $P=0.01$ .

FMRI time courses from four regions were shown. The normal FMRI response is delayed and dispersed, however by deconvolving the response the true timing of brain activation can be resolved.

Significant regions seen are: fusiform gyrus (FG); reception, recall, and match. Medial temporal lobes (MTL); recall and match. Left supramarginal gyrus (LSMG); retention, recall, and match; medial frontal gyrus (MFG) all parts. Thus FMRI can be used for short cognitive events.

#### HEREDITARY MOTOR AND SENSORY NEUROPATHY - LOM (HMSNL)

P K Thomas, L Kalaydjieva, R H M King, Edith Cowan University, Perth, WA, Australia and London University, London, UK.

An autosomal recessive peripheral neuropathy associated with deafness was initially identified in the Gypsy community in the town of Lom on the Danube in north west Bulgaria. Subsequently the disorder has been recognised in Gypsies in other Balkan countries. The onset is in the first decade and most affected people are severely disabled by the fifth decade. Deafness is invariable and usually begins in the third decade. Examination shows sensorineural deafness, distally accentuated muscle wasting and weakness, tendon areflexia, distal sensory loss and foot and hand deformity. Motor nerve conduction velocity is severely reduced, in the demyelinating range, and sensory action potentials are depressed or absent. Brainstem auditory evoked potentials show increased interpeak latencies, suggesting demyelination. Sural nerve biopsies from advanced cases demonstrate a demyelinating neuropathy with poorly developed hypertrophic changes. The features in early cases have not yet been examined. Genetic studies have mapped the responsible gene to chromosome 8q24. Link-

age to approximately the same region has recently been reported in a black American family with autosomal dominant Dejerine-Sottas neuropathy, raising the possibility of allelic mutations in a novel myelin gene on chromosome 8q24. No myelin genes are currently known to be located at this site.

#### CHILDREN WITH CEREBRAL PALSY HAVE NORMAL DEVELOPMENT OF RECIPROCAL INHIBITION

S McDonough, S Miller, J A Eyre, Newcastle upon Tyne University, Newcastle upon Tyne, UK.

**Introduction**—Cocontraction of antagonist limb muscles is prominent in infancy, persists in those with cerebral palsy, but is not characteristic of adult onset spasticity.

**Hypothesis**—Reciprocal inhibition is not mature at birth and fails to develop in those with perinatal brain damage.

**Subjects**—(1) Cross sectional study in 100 normal children (32 weeks gestation to 4 years) and 20 adults; (2) longitudinal study (12 months) of 30 normal neonates and 10 at high risk for spastic cerebral palsy. Ethical approval and written informed consent were obtained.

**Methods**—Reciprocal inhibition to contracting biceps was evoked by mechanical taps to the relaxed tendon of triceps brachii at intensities selective for group IA afferents. The taps were delivered in pseudo-random binary sequences of 1.3 s duration, which were cross correlated with the surface EMG of biceps brachii.

**Results**—In both studies of normal subjects reciprocal inhibition was shown in 30% at birth and in all by 9 months. The 10 high risk babies (four with spastic tetraparesis at 12 months) demonstrated the same normal developmental pattern.

**Conclusion**—Cocontraction in cerebral palsy is not a consequence of failure of reciprocal inhibition.

#### DISORDERED HETERONYMOUS GROUP 1A MUSCLE REFLEXES IN SUBJECTS WITH BRAIN DAMAGE ACQUIRED PERINATALLY AND IN ADULTHOOD

V M McLelland, J A Eyre, S Miller, Newcastle upon Tyne University, Newcastle upon Tyne, UK.

**Introduction**—Persistence of aberrant reflex responses in subjects with perinatal brain damage suggests that not only the descending control of reflex activity, but also the development of appropriate spinal reflex connections are disrupted. This hypothesis was tested for heteronymous reflexes between antagonist muscle pairs at the elbow and shoulder.

**Adult subjects**—24 normal, 10 with cerebral palsy (six tetraparetic, four hemiparetic), 10 subjects with spastic hemiplegia after stroke.

**Methods**—Heteronymous reflex responses were recorded in the surface EMG of biceps and triceps brachii, posterior deltoid and clavicular pectoralis major. Heteronymous excitatory and inhibitory reflexes were recorded in turn from each muscle contracting to 10% MVC, while the tap was applied to the relaxed tendon of the other muscles. The taps were delivered in pseudorandom binary sequences of 1.3 s duration, which were cross correlated with the EMG, providing for each subject up to 36 trials for each muscle combination.

**Results**—The frequency of heteronymous excitatory and inhibitory responses was calculated for each muscle combination. In

normal subjects inhibition was predominant between antagonist muscles, but an equal probability of excitation and inhibition between elbow and shoulder muscles was found. In cerebral palsy the frequency of heteronymous inhibitory responses was reduced and there was an abnormal increase in excitatory reflexes. In stroke there was a reduction of the frequency of both excitatory and inhibitory heteronymous reflexes.

#### EPILEPSY SURGERY, VISUAL FIELDS, AND DRIVING

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**Aims**—The United Kingdom DVLA regulations stipulate “the minimal visual field for safe driving is a field of vision of at least 1200 on the horizontal using the Goldman perimeter 1114e setting (or equivalent). In addition, there should be no significant field deficit in the binocular field which encroaches within 200 of fixation above or below the horizontal meridian.” The aim of this study was to ascertain how many patients after temporal lobe resection fail the visual field criteria for driving.

**Methods**—23 patients (12 women, 11 men; mean age 33.4 years, range 21 - 47) who had undergone temporal lobe resection for epilepsy were randomly selected. The underlying diseases were: hippocampal sclerosis (HS) (17), non-specific gliosis (two), angioma (one), DNET (one), and low grade glioma (two). They underwent perimetry using the Goldman 1114e setting and the Estermann binocular field assessment.

**Results**—10/23 (43%) had normal fields. There were no significant differences in the presence of a field deficit between those with HS and those with other diseases ( $C2=0.11$ ,  $P=0.9$ ). 6/23 (26%) had field deficits but passed the driving criteria. 7/23 (30%) had deficits which failed the driving criteria. 3/23 (13%) of patients were fit free but failed the field criteria for driving.

**Discussion**—A significant number of patients who have undergone temporal lobe resection will not be eligible to drive in the United Kingdom because of significant field deficits even if they are rendered fit free.

#### SAMPLE SIZE CALCULATIONS FOR MRI OUTCOME PILOT TRIALS IN MULTIPLE SCLEROSIS: RELAPSING-REMITTING VERSUS SECONDARY PROGRESSIVE SUBGROUPS

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Serial brain MRI is widely used in pilot studies of new agents to monitor treatment efficacy in relapsing-remitting (RR) and secondary progressive (SP) multiple sclerosis (MS) subgroups. For pilot trials, separate sample size calculations for the SP subgroup are currently not available. The present study considers this issue.

The calculations are based on data from six months of monthly T2 weighted and gadolinium enhanced MRI in 31 RR and 28 SP untreated patients undergoing natural history studies. The calculations are for a placebo controlled, parallel groups design lasting six months. The sample sizes are based on boot strap analysis with an 80% likelihood of showing a given treatment effect.

With a single baseline scan, demonstration of a 70% reduction in newly active lesions requires  $2 \times 30$  RR and  $2 \times 50$  SP patients. With

an extra baseline scan one month before treatment, the samples sizes are 2×20 for RR and 2×30 for SP patients.

This study shows an important difference in the pattern of longitudinal MRI activity in RR and SP groups. The sample sizes required for RR patients are comparable with previous studies. Larger sample sizes are needed for the SP group, and an extra baseline scan results in a reduction in both groups. These data should be considered in planning pilot MRI outcome trials.

#### C REACTIVE PROTEIN AND OUTCOME AFTER ACUTE STROKE

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**Background**—Raised C reactive protein (CRP) is a marker of risk in acute coronary syndromes and may represent an inflammatory element of atherosclerotic lesions. The effect of CRP on stroke outcome was studied.

**Methods**—Consecutive admissions to an acute stroke unit had blood analysed for CRP concentration within 72 hours of admission. Data on risk factors, stroke type, and severity were collected. Patient outcome was determined by record linkage to the Scottish Deaths Register. Survival and cause of death were analysed.

**Results**—263 of 283 patients had a stroke; 240 had ischaemic stroke, and 23 haemorrhage. Survival was significantly worse in those with CRP above the mean ( $P=0.0003$ , log rank test). In a Cox proportional hazards model, CRP concentration predicted survival independently of stroke severity, blood glucose, and age ( $P=0.05$ ), a more definite relation being demonstrable for those with ischaemic stroke only ( $P=0.02$ ). The cause of death certified was stroke or myocardial infarction in most patients.

**Conclusions**—Raised CRP within 72 hours of admission predicts survival after stroke. As deaths were predominantly due to atherosclerotic disease this is consistent with a hypothesised role of inflammation in the pathogenesis of acute coronary and cerebrovascular syndromes and may be a useful clinical marker for aggressive intervention.

#### DYSARTHRIA CAN CONCEAL DYSPHASIA IN MOTOR NEURON DISEASE

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Cognitive impairment is not usually regarded as part of the core syndrome of motor neuron disease (MND). Nevertheless, a few patients have overt dementia, typically frontal type or progressive aphasia. Speech in MND is often restricted by prominent bulbar symptoms. The question of whether dysphasia may also impair communication was considered.

16 consecutive patients presenting to a district neurology service over three years with a new diagnosis of MND fulfilling research criteria were assessed with a comprehensive battery of standardised neuropsychological tasks. Particular attention was paid to semantic and syntactic aspects of language production and comprehension.

Four of 16 patients (31%) became mute during the course of the study. Of these, three (19% of total; 75% of mute MND) had demonstrable language impairment. Only one reported word finding difficulties at the

time of diagnosis. The other two denied language difficulties whereas their relatives ascribed all communication problems to deteriorating articulation. One non-mute patient (1/12) performed outside normal limits on language tests in the context of more generalised changes consistent with a frontal dementia. The other 11/12 patients performed normally.

It is concluded that dysphasia is more common in MND than is generally appreciated, particularly in mute subjects, but can be missed because of prominent bulbar symptoms.

#### CONJUGAL MULTIPLE SCLEROSIS

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There has been no previous systematic study of conjugal MS. The study of conjugal pairs with complex traits provides valuable information regarding disease transmissibility and the genetic contribution to disease frequency and clinical course.

Forty five conjugal pairs concordant for MS were studied; clinical features were compared in 33 where neither partner had symptoms before social introduction; 86 offspring were individually assessed for clinical evidence of neurological disease and those over the age of 16 underwent cranial MRI. There was no evidence for clinical concordance, clustering at year of onset, or distortion of the expected pattern of age at onset in the second affected spouse. Five of 86 offspring (5.8%) were concordant for MS, four of 86 (4.7%) reported isolated episodes of neurological dysfunction. Six of 39 (15.4%) offspring had MRI abnormalities which fulfilled criteria for the diagnosis of MS. Three others (7.7%) had lesions consistent with demyelination not meeting these criteria. In total 14% had some evidence of disease.

The recurrence risk in children of conjugal pairs is significantly higher than recurrence risks for offspring of single affected parents (1:200). The risk for developing MS is evidently inherited from both parents and this argues against genetic heterogeneity. There is no evidence for a transmissible agent or for a genetic effect on clinical course or severity.

#### AUDIT OF AN EMERGENCY CLINIC IN NEUROLOGY

N Robertson, S Shaunak, D A S Compston, Neurology Unit, University of Cambridge, Cambridge, UK.

Effective triage of primary care referrals is an essential part of neurology service management. In a retrospective analysis of selected patients reviewed in a rapid referral clinic the effectiveness of identifying patients with serious abnormalities requiring urgent assessment was analysed. Statistical correlation with symptom groups was presented and the effect of such a clinic on auxiliary services was evaluated.

Twenty five per cent of telephone referrals from primary care physicians led to identification of patients considered suitable for urgent evaluation; 323 patients were assessed over an 18 month period. After neurological review relevant abnormalities were identified in 73% and 33% were considered to have warranted urgent assessment. In addition 74% required radiological evaluation and

14% had a neurophysiological procedure; 17% of patients were admitted on the same day, 13% underwent CSF analysis, and 34% required some form of therapeutic intervention. In retrospect, patients with a clinical history of greater than 11 days rarely warranted urgent referral. Visual failure and diplopia provided highest correlations for patients considered to have required urgent assessment and syncope and headache the lowest. Despite the number of patients reviewed, no effect was demonstrated on waiting times for standard outpatient review.

This work provides effective guidance to those clinicians involved in patient triage and assesses the burden of providing such a service.

#### IS RUPTURE OF CAROTID ATHEROTHROMBOTIC PLAQUE DETERMINED BY LOCAL OR SYSTEMIC FACTORS?

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The risk of ischaemic stroke distal to an atherothrombotic carotid plaque is increased if the plaque surface is irregular. Likewise, acute cardiac ischaemia is almost invariably associated with an irregular or ruptured coronary artery plaque. The risk of major vascular events in the territory of a diseased artery seems to be determined as much by the stability of atherosclerosis as by its extent. Plaque stability is considered to be determined by local factors such as sheer stress or intraplaque ischaemia, but may also be influenced by systemic factors. To test the hypothesis that plaque stability is constitutional, angiograms of 3007 patients with recently symptomatic carotid stenosis in the European Carotid Surgery Trial were studied. Plaque surface morphology in the symptomatic carotid artery was compared with that in the contralateral carotid artery, and related carotid plaque surface morphology to the risk of non-stroke vascular death during follow up. Plaque surface irregularity in the symptomatic carotid artery was highly predictive of irregularity in the contralateral carotid artery (risk ratio=2.57, 95% CI=2.12-3.12,  $P<0.0001$ ), and was associated with an increased risk of non-stroke (mainly cardiac) vascular death (log rank,  $P<0.0001$ ). It is suggested that plaque instability is constitutional. Further research is required to determine whether or not it is modifiable.

#### PATTERNS OF LONG ASCENDING PROPRIOSPINAL REFLEXES IN SHOULDER MUSCLES IN HUMAN SUBJECTS AFTER ELECTRICAL STIMULATION OF LOWER LIMB NERVES

M Saweirs, J A Eyre, S Miller, Newcastle upon Tyne University, Newcastle upon Tyne, UK.

**Introduction**—In neonatal and adult subjects percutaneous magnetic stimulation of lumbosacral nerve roots evokes excitatory and inhibitory responses in surface EMGs of upper limb muscles at latencies sufficiently brief to be compatible with propriospinal transmission.

**Aim**—to determine if lower limb nerves contributed differentially and in a functional pattern to these long propriospinal reflexes.

**Subjects**—Eleven normal adults. Ethical permission and written, informed consent were obtained. Responses were recorded in the surface EMG of ipsilateral pectoralis

major (Pmaj) and deltoid (Pdelt) muscles, during isometric contraction at 10% MVC, in response to electrical stimulation of femoral, tibial and common peroneal nerves, at 1.2 times motor threshold.

**Results**—Responses obtained in Pmaj and Pdelt had early (12–30 ms), intermediate (40–60 ms), and late (70–100 ms) excitatory and inhibitory components. In three subjects tested, the onset latencies of the early responses were 2.7–3.3 ms longer than estimates of minimum long propriospinal latencies, suggesting disynaptic or oligosynaptic linkage in a fast conducting propriospinal pathway. A pattern of responses emerged: (1) a greater probability of excitatory and inhibitory responses occurred in Pdelt (2) early excitatory and inhibitory responses were more often evoked than intermediate and late responses with all three lower limb nerves (3) the common peroneal nerve is more likely to mediate responses than tibial or femoral nerves.

#### LINKAGE IN MULTIPLE SCLEROSIS

S J Sawcer, H B Jones, R W Feakes, J Gray, N Smaldon, S J S Chataway, N Robertson, D Clayton, P N Goodfellow, D A S Compston, University of Cambridge, Cambridge, UK.

There is now overwhelming evidence that susceptibility to multiple sclerosis involves genetic factors. In the light of this we have screened the entire human genome for evidence of linkage and have identified several potentially linked regions. In the first stage of this screen 311 microsatellite markers were typed in 129 families. Twenty regions showing some evidence of linkage to disease were identified. In the second stage 69 markers from 16 of these regions were typed in a further 98 families. The evidence for linkage increased in four regions. The analysis was performed using the multipoint sib pair linkage program MAPMAKER/SIBS and the significance of the results was established using computer simulations. The strongest evidence for linkage was found on chromosomes 17q22–24 and 6p21 (the major histocompatibility complex). In addition, linkage disequilibrium at the TNFA marker from the 6p21 region was also detected. On the X chromosome evidence for linkage in male-male pairs suggests a possible X linked dominant component to the disease.

This is the first genome screen to be completed in any neurological polygenic disease.

#### REFLEX, SENSORY EVOKED, STIMULUS SENSITIVE EPILEPSY: CURRENT VIEWS

D F Scott, Retired from Royal London Hospital, London, UK.

A study was undertaken to test the personal impression that there had been changes in the frequency, type, and antiepileptic drug response for this condition over the past 30 years. Three lines of approach were used, a literature search, letters to various experienced consultants (n=12), and a questionnaire distributed to a joint neurological and epilepsy meeting (n=40). The literature search showed a change in types of epilepsy reported—for example, the appearance of seizures following video games and after calculation using traditional Japanese calculators.

Taking the results from the letters and questionnaires together, no change was reported by just over half. The remainder were

either equally positive or uncertain. Apart from photosensitivity, no change in type was reported by the majority. Considering the antiepileptic response, half reported change with newer anticonvulsant drugs and this was stronger in the personal letters to those selected because of their particularly detailed experience. Additional comments were also produced by many of those who replied to the questionnaire, suggesting that sodium valproate was particularly effective in photosensitive patients, with an additional comment about lamotrigine, either alone or in combination. These findings might explain the initial impressions.

#### MOLECULAR PATHOLOGY OF FAMILIAL ALS WITH SOD-1 GENE MUTATIONS

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**Background**—Mutations in the gene coding for Cu/Zn superoxide dismutase (SOD-1) are found in 20% of patients with familial amyotrophic lateral sclerosis (FALS). It is not known how these mutations lead to selective degeneration of upper and lower motor neurons.

**Aims**—To investigate the molecular pathology of FALS with SOD-1 gene mutations to clarify the mechanisms of neuronal death.

**Methods**—Brain and spinal cord were removed from two FALS patients with point mutations in the SOD-1 gene at codons 48 and 101. Frozen and paraffin embedded sections were processed for immunohistochemistry, with a range of anticytoskeletal protein antibodies, and for electron microscopy.

**Results**—Neurofilamentous accumulations and ubiquitin immunoreactive inclusions were found in both cases. In one these were confined to the motor neurons in the brainstem and spinal cord, in the other they were also present in pyramidal cells of the motor cortex. Electron microscopy disclosed bundles of neurofilaments I within anterior horn cells. There was no evidence of accumulation of SOD-1, SOD-2, or tau proteins.

**Discussion**—The cytoskeletal pathology of familial ALS with SOD-1 mutation falls within the range of all ALS pathology. The toxic accumulation of mutant SOD-1 is unlikely to be directly responsible for motor neuron injury.

#### IMMUNOLOGICALLY SILENT INFLAMMATION INDUCED BY CNS VIRUSES

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**Aim**—To assess if specific immunity is required for inflammation induced by CNS viruses

**Methods**—C57BL/10 mice were inoculated with the non-neurovirulent influenza virus A/NT/60/68 either directly into the caudate nucleus or into the lateral cerebral ventricle. An assessment of local and systemic antiviral immunity was made using proliferative responses, cytotoxic T cell assays, enzyme linked immunosorbent assay (ELISA), flow cytometry, and immunohistochemistry.

**Results and discussion**—Virus inoculated into the brain parenchyma was immunologically silent in most mice 10 and 90 days after inoculation. By contrast, virus inoculated into the lateral ventricle was highly immunogenic. Although a lymphocytic inflammatory reac-

tion was induced at both sites, only lymphocytes isolated from the brains of mice inoculated with ventricular virus were antigen specific. Activated antiviral CTL were purified from the brains of mice given a simultaneous parenchymal and intranasal challenge, indicating that the environment of the brain parenchyma was not inducing tolerance. Although most immigrant T cells were CD44hi and CD62Lhi and were thus activated or memory cells, a proportion were CD44hi and CD62Lhi and were therefore not activated.

These results indicate that inflammation can be induced by virus in the CNS even in the absence of specific antiviral immunity.

#### REGENERATING OLIGODENDROCYTES AND REMYELINATION IN MULTIPLE SCLEROSIS

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**Aims**—To determine the possible contribution of mature oligodendrocytes to remyelination in multiple sclerosis (MS) lesions.

**Methods**—Adult rat glia were studied in vitro, in coculture with neurons, and after transplantation into demyelinated rat CNS lesions.

**Results**—Adult oligodendrocytes and their progenitors survive and proliferate under the influence of neurons in vitro, an effect emulated by growth factors in neuronal culture. When adult glia are transplanted into demyelinated lesions, only proliferative cells contribute to the repair, and non-dividing cells fail to survive. When lesions are irradiated after transplantation, to kill dividing cells, non-myelinating oligodendrocytes are able to survive in the lesions. The interactions of regenerating mature oligodendrocytes and neurons were therefore studied. Neurons inhibit mature oligodendrocyte processing, while permitting progenitor derived oligodendrocytes to extend complex processes. Dividing oligodendrocytes can be identified; however, they are derived from differentiating progenitors, rather than regenerating oligodendrocytes.

**Discussion**—Postmitotic mature oligodendrocytes do not have the attributes necessary for remyelination. It is hypothesised that their absence from remyelinated lesions reflects limited access to survival factors through poor association with axons, as well as growth factor utilisation by dividing progenitors. Thus mature oligodendrocytes may play no part in remyelination in MS, and their presence in lesions may reflect the absence of the conditions required for remyelination.

#### A CLINICAL ROLE FOR 99mTc-HMPAO SPECT IN THE DIFFERENTIAL DIAGNOSIS OF DEMENTIA

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<sup>99m</sup>Tc-HMPAO single photon emission computed tomography (SPECT) is increasingly used as a clinical tool in the diagnosis of dementia. However, its precise contribution in differentiating forms of dementia has not previously been quantified. Three hundred and sixty three dementia patients referred to the Cerebral Function Unit at Manchester Royal Infirmary were grouped on the basis of neuropsychological, neurological, and CT findings. The diagnostic gain of <sup>99m</sup>Tc-HMPAO SPECT for the more commonly

encountered forms of dementia was determined by calculating the likelihood ratios of pairwise intergroup comparisons for different patterns of cerebral blood flow (CBF) abnormality. To quantify the clinical value of  $^{99m}\text{Tc}$ -HMPAO SPECT, average likelihood ratios were calculated weighted according to the prevalence of CBF patterns.  $^{99m}\text{Tc}$ -HMPAO SPECT was found to provide diagnostic gain for all intergroup comparisons. It was most useful in distinguishing Alzheimer's disease and Lewy body dementia from frontotemporal dementia, and least useful in differentiating between Alzheimer's disease and Lewy body dementia, and between vascular dementia and frontotemporal dementia. Study results provide a guide both to the optimal usage of  $^{99m}\text{Tc}$ -HMPAO SPECT and the interpretation of individual test results.

EFFECT OF LAMBERT-EATON MYASTHENIC SYNDROME (LEMS) ANTIBODIES ON TRANSMISSION FROM POSTGANGLIONIC PARASYMPATHETIC NEURONS IN THE MOUSE BLADDER

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LEMS patients produce antibodies to P, Q, and sometimes N type voltage gated calcium channels (VGCCs) which have been implicated in the impaired skeletal neuromuscular transmission. The cause of the autonomic symptoms in LEMS has not been investi-

gated. The aim of this study was to investigate a possible antibody mediated mechanism for the autonomic symptoms by studying transmission from parasympathetic neurons innervating the bladder of mice passively immunised with LEMS IgG. Mice were injected with IgGs (coded) from pooled controls (PC; n=10), a healthy subject (HC; n=10), a patient with myasthenia gravis (MG; n=8), and four LEMS patients: LE1-4 (n=8 of each). Strips of bladder dome were mounted in organ baths and electrically evoked contractions recorded in the absence and presence of conotoxin GVIA, agatoxin IVA, and conotoxin MVIIC (N, P, and Q type VGCC blockers respectively). Contraction amplitudes were significantly less in LE3 and LE4 than in controls. Transmitter release from PC, HC, and MG bladders involved N, P, and Q type VGCCs. Transmitter release coupled to P and Q type VGCCs was decreased in all mice treated with LEMS antibodies. This suggests that LEMS IgG reduces parasympathetic transmission through down regulation of VGCCs and this may underlie the autonomic symptoms of the disease.

PERIPHERAL AND CENTRAL RESPONSES TO HIGH FREQUENCY NERVE STIMULATION USING A DECONVOLUTION TECHNIQUE

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Using standard averaging techniques, the maximum rates of stimulation at which sensory action potentials (SAPs) and cortical somatosensory evoked potentials (SSEPs) can be obtained are limited by the fact that successive responses overlap at rates of  $>1/t$  stimuli/s, where t is the total duration of the response in seconds. In practice, this limit may be up to 300 stimuli/s for SAPs and 20 stimuli/s for SSEPs. The investigation of rate dependent conduction block in peripheral and central lesions might be facilitated if this effect could be overcome. Faster stimulus rates would also allow SSEPs to be derived more rapidly, which may be of practical benefit in operative monitoring.

Various fast stimulation protocols for brainstem evoked potentials and SSEPs have been described. Median SAPs and SSEPs at stimulus rates of at least 1280 and 160 stimuli/s respectively in normal subjects have recently been obtained using quasirandom binary stimulus trains known as maximum length sequences. The overlapped records are deconvolved to obtain the response that would have been obtained using conventional slow averaging.

Patients with focal and generalised peripheral neuropathies and multiple sclerosis are currently being studied to determine whether this rapid stimulation technique can detect conduction abnormalities covert to those methods currently employed.

## BOOK REVIEWS

### Primer on Cerebrovascular Diseases.

Edited by K M A WELCH, LOUIS R CAPLAN, DONALD J REIS, BO K SIESJO AND BRYCE WEIR. (Pp 823; PB: \$79.00, HB \$139.00). San Diego: Academic Press, 1997. ISBN: PB 0-12-743171-3, HB 1-12-743170-5.

This book's reputation preceded its arrival on my desk with the news that Boston Spa already had a six month waiting list before it was on general release. What did one expect? My dictionary says a primer is an elementary reading book for children, a short introductory book. This hardly prepared one for the 61b 2oz, 822 page encyclopaedia boasting 195 chapters written by 275 authors.

Its philosophy is admirable offering basic science for the clinician, and a clinical account for the basic scientist. The editorial guidelines should perhaps have been more rigorous, as some contributions have offered brief albeit expert overviews whilst others have produced a manuscript that would have graced a plenary lecture at a specialist conference. Section editors should have offered brief orientating introductions. The same topic appears in more than one "chapter" a duplication that somehow does not illuminate the subject in the way that it does when a debate is formally set up. There are gems, however, and nowhere else can one read about blood flow, the blood brain barrier, acidosis, excitotoxins, calcium, free radicals, and nitric oxide, etc, alongside cardiac embolism, aneurysm surgery, thrombolysis, the dose of aspirin, and rehabilitation etc. The list of contributors is a who's who of mostly North American experts. Some will claim that there are better texts in which to look up evidence based advice on management, or the latest animal model experiments, but the insistence that the two aspects of cerebrovascular disease belong together deserves to make this volume a success despite its cost. This whole area is at last moving rapidly so read it soon or wait for the next edition!

MICHAEL HARRISON

**Brain Imaging in Psychiatry.** Edited by SHŌN LEWIS AND NICHOLAS HIGGINS. (Pp 326; £69.50). Oxford: Blackwell Science, Oxford 1996. ISBN 0632036478.

Major books on neuroimaging have been published during the past few years, the earlier ones focusing on basic sciences and the more recent on neurology and neuropsychology. There have not been many on psychiatry. Furthermore, most have come from across the waters.

This has been put right by this major multiauthored book, put together by Shōn Lewis, a Professor of Psychiatry and distinguished neuropsychiatrist himself, and Dr Higgins, a neuroradiologist. As far as this reviewer knows, it is the first of its nature to be produced in the United Kingdom. The first nine chapters are dedicated to the principles and basic sciences of the main techniques including EEG topographical

mapping and magnetoencephalography. Particularly detailed are the chapters on structural MRI and MRI neuroanatomy that occupy about 25% of the book! The chapter on functional brain imaging by Professor Lewis is rather short but about the only one explaining SPECT and PET scanning.

The remaining seven chapters are on clinical applications and their content is bound to reflect ongoing interest in, and preference for, some diseases. Thus, there are two chapters on schizophrenia: one on structural imaging (including bits on the affective psychosis) and the other on functional imaging. The chapter on the affective disorders includes a useful discussion of what does it mean "to map the emotions". Chapter 13, entitled "structural brain imaging in neuropsychiatry" returns to basic principles and then deals with Alzheimer's disease, vascular dementias and Huntington's disease. Then follows a useful chapter on the functional neuroimaging of the aging brain and dementia. The last two chapters cover functional neuroimaging in the neuroses and in child psychiatry.

All books have shortcomings and the one under review is not an exception. Contributors may not deliver on time or cover well their commissioned topic, and this causes the unavoidable lack of balance, repetitiousness and sense of inconclusiveness characteristic of most multiauthored books. Then there is the rate of progress, which in the case of neuroimaging is high, and tends to render books out of date even before their publication. More serious, however, are two omissions which I am sure can be put right in the second edition.

One concerns the need to include a chapter dealing with the conceptual demands that neuroimaging is imposing on psychiatry. Central to this challenge is the fact that most mental symptoms are described at a level of resolution which is incommensurate with the quantitative requirements of functional neuroimaging. It is often forgotten that current psychopathological descriptions were constructed to meet the needs of 19th century gross anatomy and microscopy and hence are categorical and with fussy spatiotemporal boundaries. Because of the high cost involved in neuroimaging, wastage and nonsensical research (as occasionally published in the literature) can only be avoided by preparing mental symptoms for their new correlational duties. Such preparation should include rethinking their boundaries in time and space, developing multidimensional models, and creating criteria that can separate symptoms whose ontology is likely to depend on biological signals from those which are patently interactional, social, and whose definition depends upon pragmatics and communication. For reasons which escape me, psychopathologists do not yet seem to have cottoned on to this need. A second omission concerns the need for a chapter on neuropsychological paradigms and task-related functional neuroimaging, and the relevance of this approach to the study of mental symptoms.

In spite of the above, this book deserves a wide readership. It is very good at explaining what these techniques are about and their limitations, and has brought together well known researchers to summarise what is currently credible and safe knowledge; some have even looked at their crystal ball to tell what is to come. Whether trainee or consultant, the psychiatrist should consult this book as it is becoming difficult meaning-

fully to talk about mental disorders or their treatment without knowing something about neuroimaging.

GERMAN BERRIOS

### The Basal Ganglia V Advances in Behavioural Biology Volume 47.

Edited by CHIHIRO OHYE, MINORU KIMURA AND JOHN S. MCKENZIE. (Pp 519; \$139.50). New York: Plenum Press, 1996. ISBN 0-306-45386-X.

There are great changes taking place in the field of movement disorders and this book which represents the proceedings from the fifth Triennial Meeting of the International Basal Ganglia Society held in May 1995 comes at an appropriate time. The ground covered in this book is more for the scientist than the neurological practitioner, but as one negotiates the seven sections and 61 chapters a number of important points are raised which are relevant both for the current and future management of basal ganglia related disorders. However these points will be lost to most neurologists and neurosurgeons because the format of the book is rather daunting with every chapter detailing the experimental design and results with usually one concluding fact per chapter. Thus the book is inefficient in its presentation of data for those not directly working in this area, which is important as most investigators who work in this field have contributed to this book and so are almost certainly in receipt of a complimentary copy. However collections of work such as are represented in this book often herald changes in clinical practice, and so it is crucial that some of these points are brought out, perhaps by the use of introductory summary chapters at the start of each section.

The book opens with a reappraisal of the anatomical connections of the basal ganglia, and makes a number of important observations. Firstly it provides a framework for the modern management of basal ganglia disorders, by providing the anatomical, physiological and pharmacological organisation of these structures. After all it was only through experimental work that the scientific basis and rationale for the newer neurosurgical approaches was defined—for example, posteroventral pallidotomy and subthalamic stimulators in Parkinson's disease. Of importance to these models of basal ganglia function are chapters which make the point that the segregated input from the cortex to the striatal complex, necessary for the parallel pathway hypothesis of basal ganglia function, is at best a gross simplification, not least because it reduces many basal ganglia structures to the level of simple relay stations. Furthermore the current models of basal ganglia dysfunction in movement disorders often omit a number of important connections, including the input to the subthalamic nucleus (STN) from the primary and supplementary motor cortical areas; the amygdalostriatal projection; a possible thalamic projection to the STN and globus pallidus and the pallidotegmental pathway. This latter projection to the tementum, especially the pedunculopontine nucleus (PPN), is significant and consists of axon collaterals from the pallidus (and nigro)-thalamic projection and maybe as important as the cortical projection of the basal ganglia in the control of movement, especially locomotion.

Whilst this first section of the book provides much anatomical data on the

shortcomings of our current models of basal ganglia function in health and disease there is a useful discussion in the second section on the pharmacology of the pathways within the basal ganglia. Two major points come out of this section. Firstly the nigral dopaminergic projection activating the striatal dopamine receptors is important not only in synaptic transmission but the long term gene expression of other neurotransmitters. Furthermore the loss of this pathway as occurs in Parkinson's disease may also lead to the loss of corticostriate and thalamostriate synapses which has implications in the therapy of this condition. Secondly a number of different neurotransmitter receptors have been isolated in the basal ganglia which may also be important in the future as targets for anti-Parkinson's disease treatment, and includes the A2a adenosine receptor, the metabotropic glutamate receptor, and cannabinoid receptors.

The advent of surgical interventions clinically in Parkinson's disease has led to some neurophysiological studies, which form the basis for the third section of the book. These studies coupled to previous experimental observations have revealed that neurons in the striatum respond maximally to movements directed at targets of interest, or at the beginning of a complex movement. This implies that the basal ganglia are involved in the interface of sensory processing (including verbal commands), motor programming, and the desire to move, and in addition may be specifically involved in learning sequence motor tasks and attention. In contrast the PPN which has always been thought to be critical in locomotion has so far only shown changes in neuronal activity relating to voluntary arm movement, at least in nonhuman primates.

The fourth section of this book deals more with the clinical disorders of the basal ganglia, especially the anatomical and physiological substrates of the tremor, rigidity and akinesia which characterise Parkinson's disease. No answers are apparent but PET data suggest the tremor is at least mediated by the pallido-thalamo (VIM nucleus) cortical pathway. Rigidity on the other hand is associated with increased activity in the internal segment of the globus pallidus (GPi) and underactivity in frontal motor areas, and there is some correlation between the degree of clinical akinesia and GPi hyperactivity. Furthermore the eye movement abnormalities of basal ganglia disease are coded for in the STN projection to the superior colliculus.

The last three sections of the book concentrate on models of basal ganglia disorders and raise a number of questions on the mode of cell death in Parkinson's disease, including discussions on apoptosis; iron-ferritin accumulation (which may be secondary to nigral cell death) and new environmental toxins (for example, tetrahydro-B-carboline TaClo). In addition there is increasing interest in the cognitive aspects of Parkinson's disease which may precede any motor manifestations, and thus be useful in studies designed to look at very early Parkinson's disease.

Overall the book is interesting if somewhat repetitive with a large number of printing errors. The figures are adequate, but not of a very high quality. It is a tome for the student of neuroscience with an interest in basal ganglia related movement disorders, rather than

the clinician wanting to catch up on some background neuroscience. This book is therefore more likely to find a home in libraries than the clinician's bookshelf.

ROGER BARKER

**Evoked Potentials in Clinical Medicine. Third Edition.** Editor KEITH H CHIAPPA. (Pp 752; £60.50). Philadelphia: Lippincott Raven, 1997. ISBN 0-397-51659-2.

The editor prefaces this third edition with reference to the continued cost effectiveness of clinical evoked potential investigations and to the impact of structural and functional imaging. The latter has served to focus the clinical application of evoked potentials, which still provide a temporal resolution greater than modern imaging techniques. In combination with medicolegal pressures in the United States, the use of intraoperative monitoring has also grown. These changes, in addition to paediatric applications and central motor conduction studies, are well described.

The book covers a broad range, with contributors from the United States and from Australia. The usual subjects are covered and each chapter is well referenced. Special attention is given to monitoring of the spinal cord and to carotid endarterectomies. There are also chapters on advanced techniques for analysis and on statistics.

I would recommend this book for its methodical approach to each subject, describing the practical background followed by the process of interpretation with respect to clinical questions. I only have one minor objection, that is the use of the term motor evoked potential to describe the compound muscle action potential produced by transcranial stimulation, which has never seemed right to me!

SIMON BONIFACE

**Endovascular Neurological Intervention (Neurosurgical Topics).** Edited by ROBERT J MACIUNAS. (Pp 333; price \$90.00). Illinois: The American Association of Neurological Surgeons, 1995. ISBN 1-879284-38-3.

This book is in the *neurosurgical topics* series and perhaps represents the final recognition of the potential role of endovascular treatment in the management of vascular lesions of the nervous system. It is a multi-author work with a wide range of authorship of American neuroradiologists and neurosurgeons active in the field. Inevitable in work such as this, it represents differing views and approaches but provides a useful overview of the subject and the principles underlying the various management techniques.

The book highlights the rapid progress and change that has occurred in the subject, in particular the rapid development of devices which have enabled endovascular interventions to extend to almost all parts of the nervous system and the contribution of technical advances in angiographic equipment and the sort of requirements that are necessary to carry out these techniques safely. Throughout the chapters the emphasis on cooperation of a neurovascular team comes through and in two final chapters John Pile-Spellman, William Young, and Lotfi Haccin-Bey present excellent perspectives on

the changes that have taken place and are likely to take place in the future in the management of intracranial vascular malformation. Robert Tarr's final chapter provides some interesting personal reflections on possible innovative treatments that may be, in future, applied to the nervous system. The difficulties of the introduction of new technology in an intensely regulated environment, the move from the laboratory, and the experimental animal into clinical work, will increasingly present organisational challenges, particularly regulatory issues and training.

This book provides a useful overview for clinicians in the neurosciences who wish to update themselves on the current and future prospects of neurological endovascular intervention.

ANDREW MOLYNEUX

**Readers might also be interested in:**

**Eyelid Myoclonias with Absences.** Edited by JOHN DUNCAN AND C P PANAYIOTOPOULOS. (Pp 122; price £18.00). London: John Libbey and Co Ltd. 1996. ISBN 0-86196-550-7.

**Immunological Alterations in Psychiatric Diseases. Vol 18.** Edited by A E HENNEBERG AND W P KASCCHKA. (Pp 117; price DEM 135). Basel: Karger, 1995. ISBN 3-8055-6384-1.

**Headache Treatment: Trial Methodology and new Drugs.** Edited by JES OLESEN AND PEER Tfelt-HANSEN. (Pp 400; price £73.00). Philadelphia: Lippincott-Raven, 1997. ISBN 0-397-51794-7.

**Neurogastroenterology.** Edited by E CORAZZIARI. (Pp 410; price DM128.00). Berlin: Walter de Gruyter and Co, 1996. ISBN 3-11-015343-2.

**Seizures and Epilepsy in Childhood: A Guide for Parents, second edition.** Edited by JOHN M FREEMAN, EILEEN P G VINING, AND DIANA J PILLAS. (Pp 320; price £33.00 HB). Baltimore: Johns Hopkins University Press, 1997. ISBN 0-8018-5498-9.

**Metabolic Encephalopathies; Therapy and Prognosis.** Edited by S DI DONATO, R PARINI, AND G UZIEL. (Pp 209; price £39.00). London: John Libbey and Co Ltd. 1997. ISBN 0-86196-489-6.

**Motor Development in Children.** Edited by E FEDRIZZI, G AVANXINI, AND P CRENNNA. (Pp 185; price £39.00). London: John Libbey and Co Ltd. 1997. ISBN 0-86196-448-9.

**Advances in Old Age Psychiatry: Chromosomes to Community Care.** Edited by CLIVE HOLMES AND ROBERT HOWARD. (Pp 284; price £45.00). Petersfield: Wrightson Biomedical Publishing, 1997. ISBN 1-871816-34-3.