**LETTERS TO THE EDITOR**

Cerebral metabolism during vegetative state and after recovery to consciousness

One way to approach the study of consciousness is to explore leisoral cases in which impairment of consciousness is the prominent clinical sign. Vegetative state is such a condition wherein awareness is abolished whereas arousal persists. It can be diagnosed clinically soon after a brain injury and may be reversible (as in the following case report) or progress to a persistent vegetative state or death. The distinction between vegetative state and persistent vegetative state is that the second is defined as a vegetative state that has continued or endured for at least 1 month. We present a patient who developed a vegetative state after carbon monoxide poisoning and in whom we had the opportunity to measure brain glucose metabolism during the vegetative state and after recovery to consciousness. Using [F]fluorodeoxyglucose (FDG) PET and statistical parametric mapping (SPM) we compared both patient’s sets to a normal control population. Our findings offer an insight into the neural correlates of “awareness”, pointing to a critical role for posterior associative cortices in consciousness.

A 40 year old right handed woman attempted suicide through CO intoxication and was found unconscious. She was treated with hyperbaric oxygen but evolved to a vegetative state diagnosed according to the following criteria: (1) spontaneous eye opening without evidence of awareness of the environment; (2) no evidence of reproducible voluntary behavioural responses to any stimuli; (3) no evidence of language comprehension or expression; (4) intermittent wakefulness and behaviourally assessed sleep-wake cycles; (5) normal cardiorespiratory function and blood pressure control; (6) preserved pupillary, oculocephalic, corneal, and vestibulo-ocular reflexes. Brain MRI performed 14 days after admission was normal. Electroencephalography showed a 6 Hz basal activity with more pronounced slowing on the left parietal regions. Auditory evoked potentials of the median nerve showed normal latency and amplitude of P14 and N20 potentials without any late cortical components. After remaining in a vegetative state for 19 days the patient regained consciousness. Her sequelae consisted of a bilateral spastic paresis of upper and lower limbs. Neuropsychological testing 1 month after admission showed an attention deficit with moderate impairment of short term memory. One year after the accident she showed a spastic gait with altered fine motor function, most prominently on the right, a slurred speech, and minor short term memory disturbances. FDG-PET was performed during the vegetative state (day 15 after admission) and after recovery to consciousness (day 57).

The control population consisted of 48 drug free, healthy volunteers, aged from 18 to 76 years (mean: 42 (SD 21) years). The study was approved by the ethics committee of the University of Liège. Informed consent was obtained by the husband of the patient and for all control subjects. Five to 10 mCi FDG was injected intravenously; PET data were obtained on a Siemens CTI 951 R 16/31 scanner in binimensional mode. Arterial blood samples were drawn during the whole procedure and cerebral metabolic glucose rates (CMRGlu) were calculated for all subjects. PET data were analysed using SPM software (SPM96 version; Welcome Department of Cognitive Neurology, Institute of Neurology, London, UK). The use of SPM to assess between subject (rather than within subject) variability is unique to alter the relevance of our results given their high degree of significance. Data from each subject were normalised to a standard stereotactic space and then smoothed with a 16 mm full width half maximum isotropic kernel. The analysis identified brain regions where glucose metabolism was significantly lower in each patient scan compared with the control group. The resulting foci were characterised in terms of peak height over the entire volume analysed at a threshold of corrected p<0.05. During the vegetative state, average grey matter glucose metabolism was 36% lower than in controls (4.5 ± 7.3 (SD 1.4) mg/100 g/min). No substantial change in mean CMRGlu was found after recovery (4.7 mg/100 g/min). During the vegetative state, significant regional CMRGlu decreases were found in the left and right superior parietal lobule; the left inferior parietal lobule; the precuneus; the left superior occipital, superior and middle temporal gyri; and the premotor and postcentral and precentral cortex (figure, yellow colour). After recovery, metabolic impairment was confined to the left and right precentral and postcentral gyri and premotor cortices (figure, blue colour).

This case report offers an insight into the neural correlates of human consciousness (at least, external awareness as it can be assessed at the patient’s bedside). Given that global glucose utilisation levels remained essentially the same, the recovery of consciousness seems related to a modification of the regional distribution of brain function rather than to the global resumption of cerebral metabolism. The main decreases in metabolism seen during the vegetative state but not after recovery were found in parietal areas, including the precuneus. This is in agreement with postmortem findings in persistent vegetative state, in which involvement of the association cortices is reported as a critical neuroanatomical substrate and with PET studies in postanoxic syndrome, in which the parieto-occipital cortex showed the most consistent impairment. The functions of these areas are manifold: lateral parietal areas are involved in spatial perception and attention, working memory, mental imagery, and language, whereas the precuneus is activated in episodic memory retrieval, modulation of visual perception by mental imagery, and attention. Our data point to a critical role for these posterior associative cortices in the emergence of conscious experience.

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Localisation of voxels in which cerebral glucose metabolism was impaired during vegetative state (in yellow) and after recovery to consciousness (in blue), compared with the control population. SPM(1) threshold was set at voxel level corrected p<0.05 and projected on the patient’s coregistered MRI, normalised to the stereotactic space of Talairach.
Electrical inexcitability of nerves and muscles in severe infantile spinal muscular atrophy

Spinal muscular atrophy (SMA) is one of the most common fatal autosomal recessive disorders, characterised by progressive degeneration of anterior horn cells. Before the advent of genetic testing, the diagnosis of SMA was based on clinical, histopathological, and electrophysiological features. In 1992, the International SMA Consortium defined diagnostic criteria of proximal SMA based on clinical findings. In SMA type I (severe; Werdnig-Hoffmann disease), affected persons have onset of symptoms before 6 months of age and are never able to sit without support. In SMA type II (intermediate), symptoms are usually manifest after 6 months, but patients are not able to walk. SMA type III (bulbospinal) is characterised by later onset of symptoms and partial preservation of ambulation. In SMA type IV (adult), symptoms are usually manifest after 21 years of age. SMA is an X-linked recessive disorder, but the disease can also occur in females due to skewed X-chromosome inactivation. The disease is caused by mutations in the survival motor neuron (SMN) gene, which encodes a protein that is required for the formation of the nuclear lamina. Mutations in the SMN gene lead to reduced expression of the SMN protein, which results in the death of motor neurons and muscle atrophy.

In addition to a homozygous deletion of 5q, infants with SMA may have other genetic alterations. For example, some infants with SMA have a deletion of chromosome 7, and some have a mutation in the gene encoding the enzyme adenosine deaminase. Other genetic alterations that have been reported in infants with SMA include mutations in the genes encoding the proteins alpha-1-antitrypsin, beta-2-microglobulin, and a disintegrin and metalloproteinase with thrombospondin motifs (ADAMTS) 12.

Typical EMG studies in those with SMA show fibrillations and fasciculations at rest and an increased mean duration and amplitude of motor units. Motor nerve conduction velocities may be slowed but are usually normal. Korinthenberg et al reported inexcitability of motor nerves in three siblings, each of whom died from SMA before 1 month of age. In addition to a homozygous deletion of exons 7 and 8 of the telomeric SMN gene, all three siblings showed a large deletion in the region that includes all alleles of the multi-copy markers Ag1-CA and C12L2, localised at the 5’ end of the two SMN gene copies. It has been postulated that the severity of disease may be correlated to the extent of a deletion involving the SMN gene and the multicity markers. The infant in our report with SMA type I showed electrical inexcitability of motor nerves as well as the characteristic alteration of the SMN gene.

Although it has been shown for some time that histological studies have shown that sensory systems are involved in SMA, electrophysiological sensory findings have been poorly reported. In both cases, DNA analysis disclosed the 5q deletion. It is uncertain whether this finding represents a distinct entity or merely the severe end of classic Werdnig-Hoffmann disease. The diagnostic criteria produced by the International SMA Consortium currently lists “abnormal sensory nerve conduction potentials” as an exclusion criterion. If our findings of absent sensory potentials in a 5q deletion establish sensory involvement of SMA, this finding should be reconsidered as an exclusion criterion by the Consortium.

In addition to the presence of proximal weakness and atrophy, hypotonia, and evidence of neurogenic alterations in EMG and muscle biopsy, in some cases, these patients also exhibited one of the exclusion criteria defined by the Consortium—for example, diaphragmatic weakness, involvement of the CNS, or arthrogryposis. Although these patients did not show the typical SMA deletion and were therefore probably not linked to chromosome 5q, they could have had point mutations. The infant in our report showed no respiratory effort after birth, indicating diaphragmatic weakness. Our finding suggests that diaphragmatic weakness should be reconsidered as an exclusion criterion by the Consortium. Review of the literature disclosed no previous reports of electrically inexcitable muscles in SMA. This phenomenon is known to occur in a few other neuromuscular conditions such as periodic paralysis and critical illness polyneuropathy. Fibretractions, as seen in the infant in our report, are commonly seen in acute denervation and are thought to be caused by perturbation of the sarcolemmal membrane, rendering it unstable. One possibility may be that the acute denervation in SMA type I can result in abnormal function of the membrane to make it electrically inex- citable. Further electrophysiological studies at the cellular level are required to delineate this interesting finding.

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1 The International SMA consortium. Meeting report. Neuromus Disord 1990; 8

Acute overdose and intoxication with carbidopa/levodopa can be detected in the subacute stage by measurement of 3-O-methyl-dopa

Although the effects of a chronic overdose with levodopa are well known, few cases of acute intoxication have been described. A particular problem in establishing a diagnosis of levodopa overdose is usually present: the patient’s life expectancy is so short that no specific test is needed to prove the diagnosis. If there is a delay in bringing an acutely intoxicated patient to hospital, perhaps due to late discovery, the blood concentration of levodopa could already be normal. Depending on the extent of the overdose, the time could be even shorter. This report describes the clinical effects and the plasma concentrations of levodopa and specific metabolites over a period of 132.5 hours after ingestion of 30 tablets of carbidopa/levodopa (50 mg/200 mg tablets).

A 76 year old patient had a pre-existing mild akinetic rigid Parkinson’s syndrome, which had been treated for the past 1.5 years with 3x1 tablets of carbidopa/levodopa (50 mg/200 mg) a day without a substantial response. The weight of the patient was 74 kg. A known chronic obstructive airway disease was treated with a home oxygen appliance. At about 8.30 pm, the patient had attempted suicide by taking 30 tablets of carbidopa/levodopa. About 0.5 hours later he was seen by his appliance. At about 8.30 pm, the patient had attempted suicide by taking 30 tablets of carbidopa/levodopa. About 0.5 hours later he was seen by his appliance. At about 8.30 pm, the patient had attempted suicide by taking 30 tablets of carbidopa/levodopa. About 0.5 hours later he was seen by his appliance. At about 8.30 pm, the patient had attempted suicide by taking 30 tablets of carbidopa/levodopa. About 0.5 hours later he was seen by his appliance.

After an empty box of Striaton (carbidopa/levodopa, 50 mg/200 mg) was found in the patient’s flat, 1 g of carbon was given by stomach tube after gastric lavage. The patient was moved to the medical intensive care unit and observed for 24 hours. The ECG showed a P pulmonale, but no other unusual features. Echocardiography showed normal right and left ventricular function with suspicion of right ventricular hypertro-
Distribution into muscles rather than metabolism may largely determine the plasma half-life of levodopa and explain why this was only slightly altered with overdose. The measured peak concentration of 66 763 ng/ml is about 30 times higher than the peak concentration to be reached after taking one tablet of carbidopa/levodopa (50 mg/200 mg). It is apparent that the 30 tablets did not interfere with absorption or lead to a gastrointestinal paralysis due to the high dose of levodopa; the relation between amount ingested and plasma concentration seems to be linear, at least in this dose range.

We conclude from these findings that in cases of suspected levodopa intoxication some hours previously, it could be important to measure the concentration of 3-o-methyldopa, so as not to overlook an overdose with levodopa, which may be due to a suicide attempt. In addition to the diagnostic uncertainty in relation to the immediate treatment of the patient, this would also have an effect on further psychiatric and psychological therapy.

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The use of olanzapine for movement disorder in Huntington’s disease: a first case report

Movement disorder is a prominent feature of Huntington’s disease and consists of involuntary and voluntary components as well as associated bradykinesia. Pharmacological treatment is problematic because of the side effects of the drugs used, which may further compromise cognitive functioning and mobility. Patients are often not subjectively aware of their movements but can be considerably disabled by them and carers are often distressed and enquire about treatment options. If drug withdrawal is considered it is important to achieve the maximum improvement in movements with the minimum of negative side effects. This paper describes the effect of olanzapine on movements when other treatment options had been ineffective or limited by side effects.

Huntington’s disease is a hereditary, progressive neurodegenerative disorder. It consists of a triad of symptoms comprising motor, psychological, and cognitive abnormalities. The motor component consists of involuntary choreiform movements and increasing difficulties with voluntary movement. The degree of the involuntary movements is variable but in some patients can be very marked. Progression over time of the movement disorder in Huntington’s disease can be monitored using the quantitative neurological examination (QNE). This measure has three subscales, an eye movement scale, a motor impairment scale (MIS) quantifying voluntary movement and an vital capacity scale measuring involuntary movement.1,2

Pharmacological control of the symptoms has been shown to be effective with dopamine antagonists,3,4 but their use is limited because of the side effects. Clozapine and the atypical antipsychotic clozapine have an effect on further psychiatric and psychological therapy.5

risperidone. This was started at a dose of 1 mg twice daily, increasing to a dose of 1 mg four times a day over a period of 2 weeks, stopped after a brief period. He developed hypoten-sion (blood pressure 100/60 mg Hg), complaining of dizziness after the initial dose. His blood pressure remained stable, although low, after this and as there was improvement in his movements the drug was continued. However, he decided to stop the risperidone after 4 months because of his subjective experience of slowed thinking and occasional dizziness. A repeated trial of sulpiride was carried out in March 1997. Sulpiride was started at a dose of 200 mg twice a day and increased to a total daily dose of 1000 mg over 2 weeks. He was on sulpiride for 4 weeks with no improvement in his movements, so it was discontinued. The patient continued to experience low mood and after the dis-continuation of sulpiride, his antidepressant drug was changed to lofeprazine commencing at 70 mg once a day and increasing after a few days to 140 mg daily. There were no changes noted in his movements during this change.

Although the patient was subjectively unaware of the extent of his movements his everyday life continued to be affected. The social venues he felt able to attend were becoming more limited and activities he wanted to pursue such as travelling abroad by air were problematic. A trial of olanzapine was then instituted. He was started on 5 mg a day in the morning. There was a marked improvement in his involuntary movements within 1 week but once again he experienced slowed thinking. However, adjusting the time of medication to the evening led to an improve-ment in this. Six months later the improve-ment in his involuntary movements is main-tained. Serial quantitative neurological examination scores are illustrated in figure 1.

In the absence of a cure for Huntington’s disease, it is very important that any interven-tions considered enhance the quality of life of the patient and improve overall functioning. It may not always be in the best interests of the patient to use drug treatments for the movement disorder. In those patients who have severe movements, however, a trial of treatment may be appropriate and continued if a clear benefit has been achieved. Neurological monitoring and the patient’s own perception of the effect of the drug must be taken into account.

The mechanism by which olanzapine may have beneficial effects is unclear. Olanzapine has been shown to have high affinity for a large number of receptors including D1, D2, D4, 5HT2A, 5HT2C, 5 HT3, α1-adrenergic, histamine H1, and 5 muscarinic receptors. This binding profile is similar to clozapine, another atypical antipsychotic drug, but substantially different to the conventional antipsychotic haloperidol.1 Preferential loss of D2 projection neurons which are involved in a feedback loop normally active in the suppression of involun-tary movements is thought to be the pathophysiologial basis of chorea in patients with Huntington’s disease.8 The D2 antagonist properties of olanzapine may explain its possi-ble benefits in the improvement of chorea. However, the effect at other receptors such as D4 may also be important, as D4 receptor density has been shown to be raised in Hunting-ton’s disease, therefore the D4/D2 ratio of activity may also be relevant. Differences in binding profile across a range of receptors may explain clinical differences in outcome when comparing different antipsychotic drugs.

This case report indicates that olanzapine may be a useful addition to the treatments for movement disorder, for some patients, and controlled trials of its use in Huntington’s disease would be welcome.

### Patient characteristics

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age at surgery</th>
<th>Sex</th>
<th>Years with PD</th>
<th>H and Y staging</th>
<th>UPDRS off-medication</th>
<th>Pallidotomy side</th>
<th>Transient side effects</th>
<th>Medication additional to levodopa</th>
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<tbody>
<tr>
<td>1</td>
<td>66</td>
<td>M</td>
<td>8</td>
<td>2/5</td>
<td>57/58</td>
<td>R</td>
<td>Slight facial paresis, swallowing problems, drooling</td>
<td>Triptofan, tiapramizep, alprazolam, apomorphine</td>
</tr>
<tr>
<td>2</td>
<td>43</td>
<td>P</td>
<td>7</td>
<td>2/2.5</td>
<td>22/24</td>
<td>L</td>
<td>Slight dysarthria</td>
<td>Trihexifendyl</td>
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<tr>
<td>3</td>
<td>48</td>
<td>M</td>
<td>15</td>
<td>2/1.5</td>
<td>55/15</td>
<td>L</td>
<td>Facial paresis</td>
<td>Pergolide, amantadine</td>
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<td>4</td>
<td>50</td>
<td>M</td>
<td>12</td>
<td>2/2</td>
<td>45/22</td>
<td>L</td>
<td>Slight dysarthria</td>
<td>Pergolide, selegeline</td>
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<tr>
<td>5</td>
<td>53</td>
<td>M</td>
<td>14</td>
<td>2.5/4</td>
<td>69/36</td>
<td>R</td>
<td>Facial paresis, hyponoia</td>
<td>Pergolide, selegeline</td>
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<tr>
<td>6</td>
<td>58</td>
<td>M</td>
<td>13</td>
<td>2.5/3</td>
<td>48/27</td>
<td>L</td>
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<tr>
<td>7</td>
<td>61</td>
<td>F</td>
<td>15</td>
<td>2.5/4</td>
<td>55/58</td>
<td>R</td>
<td></td>
<td>Clozapine, tiapramizep, clopirdine</td>
</tr>
</tbody>
</table>

*H and Y=Hoehn and Yahr; †UPDRS off-medication scale part 3 (motor examination), in a standardised off state, 12 hours without anti-parkinson medication; ‡UPDRS not performed.*


**Transient hiccups after posteroventral pallidotomy for Parkinson’s disease**

Hiccup is defined as an abrupt intermittent, involuntary, contraction of the diaphragmatic and external (inspiratory) intercostal muscles, with inhibition of expiratory intercostal activity. This results in a sudden inspiration, abruptly opposed by closure of the glottis. This results in a sudden inspiration, abruptly opposed by closure of the glottis. Hiccups are defined by an abrupt intermittent, involuntary, contraction of the diaphragmatic and external (inspiratory) intercostal muscles, with inhibition of expiratory intercostal activity. This results in a sudden inspiration, abruptly opposed by closure of the glottis. Hiccup may result from various structural or functional disorders of the medulla, the afferent or efferent nerves to the respiratory muscles, and the gastrointestinal tract.9,10 Newson Davis performed a study of hiccup with electrophysiological techniques and concluded that hiccup is served by a supraspinal mechanism distinct from that generating rhythmic breathing.9 The principal site of interaction of the hiccup discharge with other descending drives to the respiratory motoneurone is at the spinal level. Neurogenic hiccup is particularly associated with structural lesions of the medulla oblongata.

Since 1994 we have performed 66 palli-dotomies for Parkinson’s disease in 60 patients. So far, we have seen transient hiccups in seven patients after the operation (table). Our target coordinates for the poster-oventral globus pallidus at the border of the medial and lateral segments are 2–3 mm anterior to the midcommissural point, 5 mm below the intercommissural line and 22 mm lateral to the midline of the third ventricle. Ventriculography was performed for target...
localisation. Patients started with a short schedule of corticosteroids (5 days) the night before surgery.

The hiccups started immediately after the operation or the next day, were intermittent, and the bouts of hiccup of six patients, with a duration of hours, resolved within 3 days after the procedure. One patient complained of yawning more often and frequent bouts of hiccup for 6 months.

Five patients were men. All patients were right handed. The mean age at surgery was 54 years and the mean duration of Parkinson’s disease was 12 years. All patients were taking levodopa. In four patients the hiccups appeared after a left sided pallidotomy. Patient 2 had a right sided thalamotomy 4 years before the pallidotomy. Patient 5 underwent a left sided pallidotomy 10 months before the right sided pallidotomy which caused the hiccups. The pallidotomies improved parkinsonism in the “off” state (table), contralateral dyskinesias, and pain accompanying Parkinson’s disease. Six patients had transient adverse events: four patients had a transient facial paresis postoperatively and two a slight transient dysarthria (table). Two patients had choreatic movements after the pallidotomy at the contralateral side which resolved spontaneously within 2 hours and is associated with a favourable surgical outcome.

Postoperative MR scans were obtained in the first six patients, and showed that in five patients the lesions were located in the posterior part of the globus pallidus pars externa (GPe) and interna (figure). In patient 5 the lesion was situated slightly more anterior in the GPe and putamen. In patient 3 there was a small separate lesion more dorsal, probably an infarct.

We never encountered hiccups in 150 other stereotactic procedures for Parkinson’s disease, such as thalamotomies or deep brain stimulation electrode implantation in the thalamus and therefore it is unlikely that medication or positive contrast medium vascularisation have not been studied; research has not focussed instead on location of the globus pallidus or a neighbouring structure may be involved in triggering hiccups.

Five months after left sided pallidotomy, MRI of patient 6: (A) transversal slice at the level of the anterior commissure and (B) 6 mm more ventral.

5 Bhatia KP, Marsden CD. The behavioral and motor consequences of local lesions of the basal ganglia in man. Brain 1994;117:859–76.
Comparison of stroke survivors with and without emotionalism, assessed in hospital 1 month after stroke

<table>
<thead>
<tr>
<th></th>
<th>No emotionalism (n=45)</th>
<th>Emotionalism (n=19)</th>
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<tbody>
<tr>
<td>GHQ-12*</td>
<td></td>
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<tr>
<td>Recovery locus of control scale</td>
<td>3.2 (2.4)</td>
<td>5.3 (3.5)</td>
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<tr>
<td>Impact of events scale intrusion subscale**</td>
<td>33.2 (5.3)</td>
<td>34.1 (5.7)</td>
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<tr>
<td>Impact of events scale avoidance subscale*</td>
<td>2.9 (4.6)</td>
<td>9.2 (6.6)</td>
</tr>
<tr>
<td>MASS Fighting spirit subscale</td>
<td>4.7 (4.6)</td>
<td>9.9 (6.1)</td>
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<tr>
<td>MASS Anxious preoccupation subscale**</td>
<td>49.1 (4.0)</td>
<td>48.5 (2.2)</td>
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<td>MASS Fatalism subscale*</td>
<td>22.2 (2.8)</td>
<td>25.2 (4.0)</td>
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<tr>
<td>MASS Avoidance subscale</td>
<td>20.0 (1.9)</td>
<td>21.3 (2.2)</td>
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<td>1.7 (0.8)</td>
<td>1.9 (0.8)</td>
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<td>MASS Helplessness/helplessness subscale**</td>
<td>10.9 (2.5)</td>
<td>14.1 (3.5)</td>
</tr>
</tbody>
</table>

MASS = Mental adjustment to stroke scale.

* p<0.05; ** p<0.01,

(\(F=15.33, p<0.001\), and avoidance (\(F=11.86, p<0.001\)); the mental adjustment to stroke scale subscales helplessness/ helplessness (\(F=11.71, p=0.001\)) and anxious preoccupation (\(F=8.05, p=0.006\)). The associations with fatalism (\(F=14.79, p=0.005\)) and avoidance (\(F=5.06, p=0.03\)) on the mental adjustment to stroke scale were no longer significant after adjustment for GHQ-12 score.

This study confirms earlier work by showing that stroke survivors with emotionalism have more other mood symptoms (here rated by the GHQ-12) than do those without emotionalism. It goes further however, in showing that they also have intrusive thoughts about their stroke of a sort similar to those reported by people with post-traumatic stress disorder.

Our study used a relatively weak between-group design, the number of patients was not large, and we cannot be sure that all co-founders were dealt with. None the less, our results suggest that future research into emotionalism could profitably concentrate not just on seeking its biological correlates, but should also explore the psychological factors which might contribute to its cause or continuation.

We thank those patients who participated in the study and the staff of local hospitals and the Leeds Stroke Database for their invaluable help. We also thank Dr Louise Dye for her statistical advice. This study was completed as part of work for the degree of DClinPsych at Leeds University (SE).

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Paraneoplastic stiff limb syndrome

Stiff man syndrome (SMS) is a rare, severe progressive motor disorder characterised by painful spasms, symmetric axial muscle rigidity, and uncontrollable contractions leading to distorted posturing. The disorder has been associated with the autoantigens, glutamic acid decarboxylase (GAD), and amphiphysin, which are cytoplasmic proteins in neurons of the CNS. A large series of patients with SMS found that most have autoantibodies against GAD, whereas amphiphysin is presumably the predominant autoantigen in paraneoplastic SMS. Recently, Bennett et al presented four patients with a stiff leg syndrome marked by progressive rigidity and spasms of the lower extremities. This group of patients tested negative for anti-GAD antibody by immunoprecipitation and demonstrated distinct electrophysiologically features. By contrast, another report described two patients with stiff leg syndrome who tested positive for anti-GAD antibody. Finally, in presenting a group of 13 patients, Barker et al proposed that the nomenclature “stiff limb syndrome” refers to the focal form of SMS when one or more distal limbs are involved; two of their patients were also anti-GAD antibody positive, but none were tested for antibodies to amphiphysin or identified as having an underlying neoplasm. We present a patient clinically consistent with the stiff limb syndrome who was found to have autoantibody to GAD and breast cancer.

A 68 year old woman presented with a 1 month history of painful spasms in her legs. Cramps were associated with tactile stimuli and emotional upset. Within weeks, inversion began at the left and then right ankle, making ambulation difficult. Her medical history was significant for Graves’ disease treated with thyrxine and radiiodine therapy, and hyperlipidaemia. She was a chronic smoker.

General examination was noteworthy for lymphadenopathy in the right axilla. Her mental status was worse during periods of lower extremity spasms, during which she became anxious, diaphoretic, and tachycardic. Cranial nerve and motor evaluations were unremarkable, but assessment of the left leg, due to painful spasms elicited by light touch, was difficult. Inversion and plantar flexion were essentially fixed at the left ankle but could be overcome on the right. Deep tendon reflexes were 3+ in the upper and lower extremities, with sustained clonus at the right ankle. Sensory examination showed the exception of hyperesthesia in the distal lower extremities, and coordination testing were grossly normal. No hyperlordosis or myoclonus was noted. Gait was limited due to ankle posturing.

The laboratory evaluation was noteworthy for a CSF with increased IgG indices (2.5, 3.4; normal, 0.2–0.8) and oligoclonal bands (5, 5) but no pleocytosis. Serological testing for anti-Hu, anti-Yo, and anti-Ri antibodies was unremarkable, and the haemoglobin A1C was 6.6 (5.6–7.7%). Skin biopsy at three sites on the patient’s leg showed diminished epidermal nerve fibre density and terminal axonal swelling distally, consistent with a small fibre sensory neuropathy. The patient would not tolerate EMG. Magnetic resonance images of the brain and the entire spinal cord were normal. Fine needle aspiration of the breast tissue right axillary mass showed a metastatic adenoacarcinoma. On an open surgical procedure, infiltrating duct carcinoma of the breast was identified. Anti-GAD antibodies were positive by indirect chemical assay and immunoprecipitation, but antibodies to amphiphysin were not detected by immunocytochemistry, immunoprecipitation, or western blotting (Dr P De Camilli, Yale University).

Ongoing therapy with clonazepam and a trial of oral dexamethasone did not improve the lower extremity symptoms. The patient’s ankle posturing continued a slow progression to marked inversion, with spontaneous extension of the lower extremity symptoms. The patient’s mental status was worse during periods of limb posturing.

Stiff man syndrome is increasingly recognised as a heterogeneous disorder. Other case reports have documented patients with “focal” disease involving either lower or upper extremity posturing, which contrast
with the “diffuse” axial and subsequent proximal muscle distribution of the classic disorder. Our patient differs from those reported with stiff leg syndrome in that an occult malignancy was present. Unfortunately, we were unable to obtain electrophysiological studies for comparison. The search for a paraneoplastic process was based on the findings of axillary lymphadenopathy and an abnormal CSF. Our patient is only the second reported patient with paraneoplastic SMS associated with anti-GAD antibody; the other had upper limb rigidity in the setting of breast cancer and additionally mounted an immune response to amphiphysin.

Paraneoplastic processes can affect any component of the nervous system and, occasionally, multiple levels, as in the syndrome of sensory neuronopathy-encephalomyelitis. Our patient’s findings were not entirely consistent with criteria for classic SMS in that an apparent encephalopathy and a small fibre neuropathy were identified—for example, her dysautonomia (tachycardia and relative hypertension) during spasms may have been a manifestation of involvement of small fibres. The role of autoantibodies in the pathogenesis of SMS and cancer is unclear. Via its probable function in endocytosis, amphiphysin has been postulated to play a part in the regulation of growth factor internalisation; however, the absence of an autoimmune response to this autoantigen in our patient suggests that other mechanisms of oncogenesis in SMS exist. Given anecdotal evidence of improvement in paraneoplastic SMS after treating the underlying malignancy, we suggest that all patients with SMS, diffuse or focal, be screened for occult cancer.

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Tetrodotoxin intoxication in a uraemic patient

Tetrodotoxin intoxication results from ingesting puffer fish or other animals containing the toxin. Clinical presentation is mainly acute motor weakness and respiratory paralysis. Death is common in the worst affected victims. Although the severity of the symptoms generally depends on the amount of toxin ingested, it may be influenced by the victim’s medical condition, as described in this report. The patient was a 52 year old uraemic woman. The uraemia was of unde fined aetiology. Over the past 3 years she has received regular haemodialysis. One day both she and her husband, a healthy 55 year old man, ate a fish soup. About 3 hours after the meal she developed a headache and a lingual and circumoral tingling sensation and numbness at the distal parts of all four limbs. She was dizzy and unsteady, had difficulty in swallowing, and became very weak. She was taken to the emergency service and was placed on machine assisted ventilation as respiratory distress and cyanosis developed. Her husband remained asymptomatic throughout this time.

The patient’s condition kept on deteriorating, developing eventually into a comatous-like state with no spontaneous or reflexive eye opening or limb movement within 30 minutes of intubation. On neurological examination, the pupillary light reflex was absent and oculocephalic manoeuvre elicited no ocular movements. All four limbs were areflexic and Babinski’s signs were absent. Brain CT and laboratory studies of arterial blood gas (under assisted ventilation), electrolytes, liver function, blood glucose, and CSF study were unremarkable. An examination of renal function indicated chronic renal insufficiency with mild azotaemia (urea nitrogen 70 mg/dl, creatinine 9.1 mg/dl). An EEG, recorded 18 hours after the onset of symptoms when the neurological condition was unchanged, showed posterior dominant alpha waves intermixing with trains of short duration, diffuse theta waves. When brief noxious stimuli were applied to the sternum, they were replaced transiently by beta activities. The findings suggested that the profound neurological dysfunction might be peripheral in origin. The patient was given a course of haemodialysis according to the set schedule for uraemia at 21 hours after onset of the symptoms. Her condition improved dramati-
cally within an hour. She could open her eyes and she communicated and answered questions correctly by blinking. Pupillary reflex recovered and voluntary eye movements were limited only at the extreme lateral gaze. Muscle power was grade 3 and 4 in the proximal and distal parts of the four limbs. Tendon reflexes were still absent. She was taken off mechanical ventilation the next day. Her clinical condition continued to improve and symptoms subsided in a stepwise pattern, although retinal blood vessels were still dilated and her deep tendon reflexes were absent. She regained her initial strength by the end of the month. She was “too weak to move” at that time. She was discharged on day 16.

When analysing the remains of the cooked fish (identified as *Yongieichthys nebulosus*), tetrodotoxin was demonstrated by thin layer chromatography, high performance liquid chromatography, and cellulose acetate membrane electrophoresis. Toxicity was assayed by using Institute of Cancer Research strain adult male mice and the toxicity score was 25 mouse units (MU)/g in fish muscle (1 MU/g in the TCR strain). Tetrodotoxin exerts its effect through binding with and blocking the voltage dependent sodium channel. The voltage clamp experiments showed that tetrodotoxin diminished the sodium inward current responsible for the depolarisation of excitatory membrane. The gating properties of the sodium channel, such as the activation and inactivation mechanism, are not altered—that is, the sodium channel is not permanently damaged and its function recovers when the bound toxin is released. In uraein, ion conductance through the sodium channel is also impaired. Sodium permeability through easily damaged membranes is reduced and small inward sodium current and reduced action potential amplitudes are noted in experimental uraein neuropathy. By contrast with the effects of tetrodotoxin, uraeinia changes the basic property of the sodium channel by an increased inactivation and an impaired activation mechanism. The excitability of peripheral nerves will be more significantly depressed when these two conditions cooperate. The synergistic effect of uraein and tetrodotoxin is obvious in this incident in which the patient and her husband ingested roughly an equal amount of toxic fish (about 200 µg, calculated from toxic score times the weight of ingested fish).

The amount is about 10% of the estimated lethal dose in humans—2200 µg/60 kg body weight (body weights of the patient and her husband were 54.5 and 62 kg respectively)—and caused no clinical evidence of poisoning in the healthy person. It was of interest that the CNS was relatively spared from the toxicity as the EEG showed a posterior dominant, promptly reactive alpha rhythm and the patient retained consciousness when the symptoms were at their most severe.

One of the most striking clinical features in our patient was the response to haemodialysis. Despite the small amount of toxin ingested, the dramatic improvement of her clinical condition was most likely attributed to the rapid elimination of absorbed toxin in the course of haemodialysis, rather than spontaneous recovery. The physical and chemical properties of tetrodotoxin are also amenable to haemodialysis. Traditionally, the management of tetrodotoxin intoxication is mainly supportive, such as gastric lavage to remove unabsorbed toxin and machine assisted ventilation when respiration is severely affected. We suggest that haemodialysis may be an effective method in the treatment of tetrodotoxin intoxication.

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**Relation between critical illness polyneuropathy and axonal Guillain-Barré syndrome**

The clinical entity critical illness polyneuropathy occurs almost exclusively in patients in critical care units and has been characterised as a complication of sepsis and multiple organ failure. Critical illness polyneuropathy may be a common cause of the difficulty in weaning patients from the ventilator, particularly those who show intractable ventilator dependence. All the measures used to prevent ventilator dependence in multiple organ failure are the main methods now used to deal with critical illness polyneuropathy. Knowledge of this type of polyneuropathy is necessary to prevent or treat sepsis and multiple organ failure are the main methods now used to prevent ventilator dependence. All the measures used to prevent ventilator dependence in multiple organ failure are the main methods now used to deal with critical illness polyneuropathy.

Critical illness polyneuropathy may be synonymous with the pathological designation of acute inflammatory demyelinating polyneuropathy (AIDP), the pathological entity Guillain-Barré syndrome often has been considered to be synonymous with the pathological designation of acute inflammatory demyelinating polyneuropathy (AIDP), the pathological entity Guillain-Barré syndrome, and suggested that there is a fundamental difference in the underlying pathophysiology, resulting in primary axonal damage rather than demyelination. Griffin et al. confirmed the existence of the acute motor-sensory axonal neuropathy (AMSAN) pattern of Guillain-Barré syndrome described by Feasby et al. Infection caused by the gram negative bacterium *Campylobacter jejuni*, a leading cause of Campylobacter jejuni infection.
of acute diarrhoea, commonly precedes the development of Guillain–Barré syndrome. There is a close association between axonal Guillain–Barré syndrome and antecedent C jejuni infection. The antecedent infectious symptom was diarrhoea in three of five patients with axonal Guillain–Barré syndrome described by Feasby et al. Observations by Griffin et al confirmed that AMSAN follows C jejuni infection. Serum samples from patients with axonal Guillain–Barré syndrome subsequent to C jejuni enteritis often have a low T cell autoreactivity to gangliosides GM1, GM1b, GD1a, or GaINAc-GD1a in the acute phase of the illness, and there is molecular mimicry between these gangliosides and the lipopolysaccharide of C jejuni. This ganglioside mimicry may trigger high production of the IgG anti-ganglioside antibodies and these autoantibodies may cause motor nerve dysfunction in patients with GBS.

Interestingly, Hagensee et al reported a case of “C jejuni bacteremia and subsequent Guillain–Barré syndrome” that occurred in a patient with chronic graft versus host disease and acute myeloid or lymphoid leukemia. Because there was acute flaccid paralysis associated with sepsis, some physicians might have diagnosed critical illness polyneuropathy. Conversely, the existence of this case strongly suggests that some diagnosis of critical illness polyneuropathy should actually be axonal Guillain–Barré syndrome or AMSAN. Our hypothesis of the nosological relation between critical illness polyneuropathy and Guillain–Barré syndrome is shown in the figure. Serum IgG antibodies against GM1, GM1b, GD1a, or GaINAc-GD1a could be used as immunological markers for axonal Guillain–Barré syndrome. To examine the aetiology of critical illness polyneuropathy and its nosological relation to axonal Guillain–Barré syndrome, it is necessary to investigate whether patients with critical illness polyneuropathy have anti-ganglioside antibodies during the acute phase of the illness.

Repetitive transcranial magnetic stimulation in the treatment of chronic negative schizophrenia: a pilot study

Recently, a new technology known as repetitive transcranial magnetic stimulation (RTMS) has been developed. In 1994, the use of magnetic stimulation in clinical psychiatry was suggested. Since then, it has been used in the study or treatment of obsessive-compulsive disorder, conversion disorder, schizophrenia, and particularly, depression.

Our pilot study aimed to assess the possible adverse effects of this treatment in chronic schizophrenic patients with severe negative symptoms; to evaluate if direct RTMS of the prefrontal cortex might improve negative symptoms or cognitive impairments in patients with chronic schizophrenia; and, thirdly, to note if RTMS might modify the deficit in prefrontal cortical activity, often referred to as hyperactivity established in schizophrenia, specially under conditions of task activation.

Six right-handed patients with chronic schizophrenia were identified at the outpatient psychiatric service of the Hospital Clinic of Barcelona. There were two men and four women (mean age 39).

Exclusion criteria included alcohol or substance abuse dependence disorder in the past 5 years, focal neurological findings, systemic neurological illness, taking cerebral metabolic activator or vasodilator medications, electroconvulsive therapy within 6 months, and significant abnormal findings on laboratory examination.

All patients were taking neuroleptic drugs, but a stable dose for at least 3 months was required. All patients were studied off benzodiazepines for at least 1 week before beginning the treatment. During the RTMS, psychotropic medications were continued at the initial dosage.

All patients were admitted to hospital. Inpatients underwent a neuropsychological battery, the day before beginning the treatment and at the end of the treatment. The UKU scale was also administered after each session.

An equivalent neuropsychological battery was used on both occasions, which consisted of the block design test of the Wechsler adult intelligence scale, the trail making tests of the Wechsler adult intelligence scale, the trail making tests, delayed visual memory achieved significance (p=0.05). This feature might be basically explained by improvement of attention, specifically of the maintenance of attention, which allows the correct function of the working memory. Thus, although there are methodological limitations regarding the power of our conclusions, it is certain that there has been an improvement in the attentional capability.

We found that all patients (except one, who was always within the normal range) diminished their number of perseverative answers (mild headache and tinnitus).

Table Neuropsychological tests and PANSS scores

<table>
<thead>
<tr>
<th>Test</th>
<th>Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Block design</td>
<td>Pre 49 (11.95) NS</td>
</tr>
<tr>
<td>Trail making test A</td>
<td>Post 50 (8.69) NS</td>
</tr>
<tr>
<td>Trail making test B</td>
<td>Pre 38 (3.4) NS</td>
</tr>
<tr>
<td>Immediate visual reproduction</td>
<td>Pre 41 (10.03) NS</td>
</tr>
<tr>
<td>Delayed visual reproduction</td>
<td>Post 50.5 (8.42) NS</td>
</tr>
<tr>
<td>Immediate verbal paired associates</td>
<td>Post 54.8 (11.2) NS</td>
</tr>
<tr>
<td>Delayed verbal paired associates</td>
<td>Pre 46.18 (2.83) p&lt;0.05</td>
</tr>
<tr>
<td>PANSS-P</td>
<td>Post 35.8 (11.84) NS</td>
</tr>
<tr>
<td>PANSS-N</td>
<td>Pre 59.5 (10.03) NS</td>
</tr>
<tr>
<td>PANSS-P</td>
<td>Post 8.8 (1.17) NS</td>
</tr>
<tr>
<td>PANSS-N</td>
<td>Post 37.67 (11.15) NS</td>
</tr>
<tr>
<td>PANSS-P</td>
<td>Pre 36.5 (11.47) p&lt;0.02</td>
</tr>
<tr>
<td>PANSS-N</td>
<td>Post 31.67 (8.26) NS</td>
</tr>
<tr>
<td>PANSS-P</td>
<td>Post 27.83 (8.47) NS</td>
</tr>
<tr>
<td>PANSS-P</td>
<td>Post 16.83 (7.28) NS</td>
</tr>
<tr>
<td>PANSS-N</td>
<td>Post 15.33 (7.55) NS</td>
</tr>
</tbody>
</table>

**Pre**=pretreatment; **Post**=post-treatment; **PANSS**=positive and negative scale; **PG**=general psychopathology scale; **Ng**=negative scale; **Ppg**=positive scale.

RTMS may be given to stable schizophrenic patients without exacerbating their psychoses. All patients tolerated the RTMS well, with minimal side effects (mild headache and tinnitus).

Neuropsychological battery, we found a general improvement in all post-treatment scores (table), but only delayed visual memory achieved significance (p<0.05). This feature might be basically explained by improvement of attention, specifically of the maintenance of attention, which allows the correct function of the working memory. Thus, although there are methodological limitations regarding the power of our conclusions, it is certain that there has been an improvement in the attentional capability.

With regard to the neuropsychological battery, we found a general improvement in all post-treatment scores (table), but only delayed visual memory achieved significance (p<0.05). This feature might be basically explained by improvement of attention, specifically of the maintenance of attention, which allows the correct function of the working memory. Thus, although there are methodological limitations regarding the power of our conclusions, it is certain that there has been an improvement in the attentional capability.

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Sensory alien hand syndrome

The case report by Ay et al of alien hand syndrome and review of the literature neglected the intriguing issue of why in every case so far reported the patient seems to be terrified of the alien limb. Not believing that you are any more in control of a limb is not likely to be a pleasant experience.

Those with alien hand syndrome seem to jump to extremely negative conclusions concerning the intent of the limb. Typically, as in the report of Ay et al, the common belief is that the limb has deeply malevolent intentions towards the victim.

It is this aspect of alien hand syndrome that I suggest also incorporates into its neurological explanations, and which provides a clue as to why our everyday experience of being in charge of our bodies, and so initiating all personal action, itself has a neurological basis. In other words, while the brain is the seat of all our thoughts and experiences, there is also a part of our nervous system which is responsible for our belief that we have free will over our behaviour. Patients with alien hand syndrome think that they are no longer in control of a limb because the part of the brain that gives us the sensation of control over our bodies has been damaged. When that happens, our limbs seem to act independently of us.

Research conducted in the 1980s has found that the same electrical brain wave changes that characteristically precede all limb movements, occur several 100 ms before we seem to consciously decide to move a limb. If our conscious decision to act is preceded by brain changes that anticipate action, then our “decision” to choose how to behave or “freedom”, as in free will, is in fact illusory. Our choices have in a sense been decided beforehand by our brains.

Spence’s evidence that such a, combined with phenomena such as alien hand syndrome, means that philosophers have to reconsider whether we have free will. He argues that these data suggest that our sense of agency is illusory and it follows that most of us share in common the useful delusion that we have free will. Patients with alien hand syndrome have lost this experience in relation to a particular limb. There is a sense then that those who experience the syndrome are closer to the reality of how much we are responsible for our actions than the rest of us.

This is because all human functions are part of the brain that normally works to make us think that we have conscious freedom of will. They develop the experience, therefore, of becoming mere remote spectators to the actions of the alien limb. Defenders of human “free will” argue what happens before the brain itself decides to act is still unknown, and there may be a role for our own autonomy there. But even these free will guardians concede the neurological research indicates that whatever happens before the brain is roused, must occur below our conscious awareness.

Yet in alien hand syndrome the patient thinks that the hand has hostile motivations; it is invariably the case that the patient not only thinks that the limb is “not self” but finds that the limb behaves towards the self in a destructive and aggressive manner. This could be explained by the assumption that we lose our conscious sense of voluntary control over our bodies, our minds have to come up with an explanation for the location of action of our movements. We decide that if ourselves are not in control, then someone or something else must be; therefore, we no longer have a sense of the limb belonging to us.

Because to lose control over our bodies is one of the most terrifying experiences, our attempt to explain this finding occurs in the context of fear. It may be that our apprehension leads us to misinterpret innocent reflexive acts of our hands, such as scratching or rubbing, as malevolently inspired. Plus it could be that our interpretation of spurious possession in turn inspires the patient himself, only this is beyond our conscious awareness.

It may therefore be that we need to believe in our own free will and personal control over our bodies, because if we did not, the experience of our bodies acting as if we were directly alone for the ride, too frightening. Also, we may no longer believe that our bodies or its relevant parts belong to us. All neurologists who have reported alien hand syndrome remark on how psychologically disturbing the symptom is for the patient. Psychiatrists would be interested in the parallels between alien hand syndrome and the personality phenomena. So the fact that every case, plus the fact that the two diseases may share corpus callosum pathology, could give some way to explaining why schizophrenic symptoms are frightening to the patient. So it seems we know that our limbs belong to us because they obey us. When they seem to stop responding to our wills, we conclude that our limbs are no longer our own, and try to fend them off. Hence it would seem that one of the prices we had to pay for conscious awareness of ourselves to evolve as a function of the brain, is the delusion that we are responsible for all our actions. If we had conscious awareness of ourselves, but no sense of free will, our bodies would feel alien to us.

The philosophical importance of alien hand syndrome is that it shows emphatically via neurology that it is possible to drive a wedge between consciousness and the experience of free will. The brain had to develop the sensation of free will after developing consciousness, because being without the sensation of free will produces extremely negative emotional experiences. So the fact that every case, so far reported of alien hand syndrome imputes negative intent to the alien limb might not be an incidental finding, but a core aspect of the disorder.

R PERSAUD


The authors reply: We appreciate Persaud’s comments regarding the alien hand syndrome, “the perceived malevolence of the affected limb towards its victim, and the question of whether with loss of the conscious sense of voluntary control over our bodies, our minds... decide that if ourselves are not in control then someone or something else must be”. We would offer that the value of our particular case is that it was due to a central deafferentation—therefore the term “sensory alien hand syndrome”. As
opposed to the idea that “we know our limbs belong to us because they obey us,” we know that our limbs belong to us because they provide us with sensory input that is recognised as self. Many patients with movement disorders or paralysis lose control of their limbs but still have no difficulty in realising that they have limbs. Indeed even in “phantom limb” there is sense of self due to central processes in the absence of a limb. Our patient, as do others with anosognosia and primary abnormalities of central sensory systems, shows perhaps that it is central sensory processes that are the key to identifying “self”. We know our limbs not because they obey us but because their pattern of sensory reactivation that accompanies our own limb movements. When this pattern never reaches specific cortical regions, then the limb is not perceived as self; called “amorphogenesis” by Denny-Brown and Banker. Selectivisation by the centrally deafferentated limb in “sensory” or “posterior” alien hand syndrome, or kinaesthetic stimuli due to movement of the limb as in the “anterior” or “posterior” alien hand syndrome, is perceived as due to another person or thing without critical questioning. This raises the most interesting question of what brain region is deafferented in the anterior alien hand syndrome wherein the sense of self due to central processes is intact.

It is not our clinical experience nor the conclusions based on published reports that all patients suffering with alien hand syndrome are affected by the left hemisphere. In one author’s experience (BHP), two patients with alien hand syndrome and related intermanual conflict were irritated by but not terrified by their opposing limbs simultaneously vying for a cigarette or book. Selectivisation by the centrally deafferentated limb in “sensory” or “posterior” alien hand syndrome, or kinaesthetic stimuli due to movement of the limb as in the “anterior” or “posterior” alien hand syndrome, is perceived as due to another person or thing without critical questioning. This raises the most interesting question of what brain region is deafferented in the anterior alien hand syndrome wherein the sense of self due to central processes is intact.

Unlike our case of limited duration, the persistence of alien hand syndrome seems dependent on mesial frontal dysfunction. These patients rarely deny that the affected limb belongs to them. Instead, they understand it in terms of their “anarchic hand”. Hence, although the initial syndrome may result in disjointed and terrifying perceptions, it seems that the brain quickly re-establishes its control by presently unknown adaptive capacities. Furthermore, why it almost exclusively involves the left side and is bilateral in right handed people remain unknown. Studying this syndrome in greater detail may yield additional insights into the pathophysiology of denial and misidentification.

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Vasomotor reactivity is exhausted in transient ischaemic attacks with limb shaking

The article of Baumgartner and Baumgartner entitled “Vasomotor reactivity is exhausted in transient ischaemic attacks with limb shaking” provides interesting new information regarding motor-related involuntary limb movements contralateral to haemodynamic failure from severe carotid artery occlusive disease. The authors evoke an “exhausted cerebral vasoreactivity in the hemispheres opposite the involuntary limb movements”. In their report, involuntary movements affected only the limbs, and displayed no tonic contraction, tonic-clonic jerking, or Jacksonian march and no epileptic activity during attacks. These findings led the authors to strongly argue against seizures as the cause of limb shaking in these transient ischaemic events.

In contradistinction, a 72 year old right hand man was admitted to our hospital with a 3 month history of episodic weakness and numbness of the right arm. The patient then had six discrete stereotypic episodes of right arm weakness and clumsiness that were also associated with difficulty in speaking. Several episodes of dysarthria, numbness and weakness of the right arm and leg (MRC grade 4/5) were seen, unrelated to posture, some of which occurred when the patient was supine. Movements were characterised by slight tremulousness and asterixis-like movements of the outstretched right arm. There was a return to baseline functioning between events. Video-EEG monitoring, however, showed low voltage spikes in the left central-parietal head regions contralateral to the facial twitching and the right arm and right leg weakness. Although ongoing clinical and EEG seizure activity stopped, after 2 mg intravenous lorazepam, they reoccurred after loading with phenytoin. Because angiography disclosed a greater than 95% stenosis of the left internal carotid artery (while the patient was treated with phenytoin at a concentration of 16.5 mg/l), the patient was anticoagulated with heparin, but episodes continued. It was only after a left carotid endarterectomy that all episodes disappeared, tremulousness, and EEG epileptiform activity stopped. They have not recurred over the past 5 years.

The literature includes several cases of focal motor inhibitory seizures causing weakness. Although it is impossible to prove a negative, it could be argued that although no epileptiform or other evidence of seizure activity is present in a particular case, the abolition of ongoing clinical and EEG evidence of inhibitory motor activity by intravenous diazepam argues in favour, at least in part, of an ictal contribution. The fact that in virtually all reported cases, abnormal movements are more definitively resolved by carotid endarterectomy, argues for an underlying ischaemic pathology that induces focal seizures. There are few reports that clearly delineate the interaction and association of inhibitory focal motor seizures and transient ischaemic attacks, as there are few sequential trials of antiepileptic drugs or anticoagulation (under EEG monitoring) and finally carotid endarterectomy. Several authors support the concept of an inhibition of motor function in parietal and secondary somatosensory regions by seizure activity which then interrupts the sensory feedback loop to motor integration with inhibition of subcortical and cortical areas.

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Baumgartner and Baumgartner reply: We are grateful for the response of Kaplan to our short report. We agree that somatic inhibitory seizures may mimic transient ischaemic attacks (TIAs). Such TIAs are associated with negative symptoms such as sensorimotor deficits and difficulty with speaking, EEG evidence of seizure activity, and ceasing of the TIAs after the administration of an anticoagulant drug. 2. Limb shaking TIAs, however, differ from TIAs related to inhibitory seizures in several ways. (1) They are associated with positive phenomena (limb shaking), and the involuntary movements do not affect the facial musculature. Patients with attacks of shaking movements of the limbs have no EEG evidence of epileptiform activity, and involuntary movements do not stop after administration of anticoagulant therapy. (3) Although the patient presented by Kaplan had a 95% stenosis of the left internal carotid artery, it is unclear whether haemodynamic failure was present or not, because no studies evaluating the haemodynamic reserve of the homolateral hemisphere were presented. This is in accordance with the finding that the involuntary movements as well as the sensorimotor deficits of Kaplan’s patient were not related to hypoperfusion. (4) The pathogenesis of limb shaking may be due to disinhibition of subcortical control mechanisms as a result of ischaemia. In our opinion, it is not clear whether the asterixis-like movements of the outstretched right arm of Kaplan’s patient are due to epileptic seizures, because unilateral asterixis of the outstretched arm has been reported with contralateral vascular lesions affecting almost all cerebral structures involved in the homolateral hemisphere. 3


BOOK REVIEWS


To the MRCP candidate neurology is one of the more daunting specialties. The unfamiliar nerve conduction study and the frankly mysterious EEG can distress an otherwise well rounded senior house officer. Despite the fact that much of neurology is commonly seen on a general medical ward—strokes, dementias and so forth—the general perception is of an unimaginable list of eponymous syndromes and obscure signs. Rather than dwell on the last, in this book Dr Smith tries to address the commoner complaints as examination style questions each with a “simple clinical les-

The “grey case” section, for instance, includes questions on multiple sclerosis, cluster headache, and HSV encephalitis, while broadening the topics to include postinfective demyelination, chronic hemi-

There is, however, a tendency for the discussion after each question to be rather brief. A fuller explanation, with more allowance for the reader’s ignorance, would have been appreciated. The data interpretation section is somewhat better, covering CSF, EEG, and other data extremely well. Perhaps a little too well; would an MRCP candidate really be expected to recognise the character-


This book, after a short introduction to some of the fundamental features of the disease goes on to provide some 117 illustrations of aspects of the disease from Cruveihier’s plates to histopathological specimens and also a heavy leaning to imaging particularly magnetic resonance imaging, as might be expected. There is no doubting the aesthetic impact of this short book. In addition, the fact that these illustrations emanate from a well established figure in the multiple sclerosis world and are likely to be a representative set of personal teaching slides from a successful academic career all vouch for the provenance and informative nature of the atlas. However the place of such a book within a neurologist’s library has to be questioned. There are a plethora of high quality textbooks devoted to all aspects of multiple sclerosis all well illus-

There follows a discussion of the different autologous donor sites and synthetic materi-

This monograph is the latest to be produced by the American Association of Neurological Surgeons as part of the Neurosurgical Topics series. It begins by tracing the history of cal-

The reconstruction of traumatic and post-

This is volume 47 of a series entitled


Ech/oencephalo
clopsis. Edited by ROBERT MACFARLANE

The clinical section covers the examination technique, normal reference values, the main categories of cerebrovascular disease, and also contains chapters on areas which may be less immediately suitable for ultrasound study. For example, the findings in head trauma, tumours, psychiatric disorders, and movement disorders are the subject of separate chapters. Although I have no prob-

As with any book with multiple authors there is some variation in style and overlap, particularly in the introductions and conclu-

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Physiologists. Most of the 45 contributors are American or British, almost half of whom, including Dr Cole, are from Southampton. The book begins with a pathological

Letters, Correspondence, Book reviews, Correction
introduction setting the scene for the five main disease sections covering developmental genetic disease, spinal injury, infection, tumour, and the effect of neurological and systemic disease on the spinal cord. This chapter covers a wide area from multiple sclerosis to motor neuron disease to vascular disease to metabolic diseases. Then follows a section on investigation considering imaging, neurophysiology, and urodynamics. Finally, there is a miscellaneous section covering clinically important entities such as pain, sexual problems, and terminal care associated with spinal cord disease but also including a highly specialised chapter on the role of spinal cord injury in those who dive frequently but without decompression illness (our fault, not theirs). The chapter on motor neuron disease being up to date and topical, malignancies being covered in depth. That on sexual problems associated with spinal cord disease is excellent, particularly practical and a must for both doctors dealing with spinal disease and for patients themselves who are often unformed (our fault, not theirs). The chapter on depression illness will be food for thought for many doctors who enjoy recre- tional diving, for although studies have not yet shown adverse affects on the quality of life in those who dive frequently but without incidence, some evidence for cumulative neurological damage from neurophysiological, imaging, and pathological studies is compelling.

The quality of illustration is high. Perhaps not surprisingly, this is particularly evident in the imaging section (where there is a rather spectacular sagittal T2 weighted MRI of a intramedullary arteriovenous malformation). In addition to imaging many of the chapters also make good use of schematic diagrams and line drawings to enhance the text.

Drs Engler, Cole, and Merton end their preface by commenting that “Our main hope, however, is that the chapters will read as a series of views on the spinal cord and its disease, so that a surgeon may learn about current practice as well as the wide range of conditions affecting the cord that are outside the field of surgery”. While I agree that educating surgeons is an admirable aim, I think that the authors rather undersell themselves and that this book’s main strength, as I have said above, is that it will appeal to all disciplines that deal with spinal cord disease, bringing together neurological, rheumato- logical, and surgical disease that is often covered in separate textbooks.

GILLIAN HALL


This is the second time that I have been asked to review a book on this topic. The first time I approached the task with some scepticism were neurological diseases in women really so different from those in men that they warranted their own text book? But I rapidly became a convert to the cause, being reminded that there are issues specific to females that influence both disease, investigation, and treatment (pregnancy, breast feeding, menopause, to name the most obvious) and that not all neurological diseases attack the sexes equally. There are also wider socioeconomic and legal issues that play a part in the complete disease picture which many of us neglect too often but which this book is careful to address (see below). Leaving content aside for a moment, this is a beautifully presented book; clearly headed and with wide use of well constructed tables. It encourages one to read on. It seems up to date and well referenced.

The contributors (40 in total) are exclusively American, and east coast American at that with only occasional forays westward. The text is divided into three sections. The first, entitled General Issues in Women includes an anatomical chapter considering the sex differences of regional brain structure and function. More novel for this type of text, it contains two thoughtful chapters considering women’s health within the context of their lifestyles and women’s health and its relation with the law. This chapter considers issues such as coercive approaches to preventing foetal harm, those relating to informed consent to medical treatment, and difficult choices with neurological implications. The law and the case examples are exclusively American but the issues are universal. This opening section leaves no doubt that this is a book that has taken female issues extremely seriously.

The second section looks at neurological diseases as they affect females at different life stages, from birth through menarche, pregnancy, and menopause, to the elderly woman. As well as considering genetic diseases that strike at a particular age, these chapters consider the influence of changing physiology and hormonal balance on neurological disease. The third section is the most conventional. Each chapter considers a neurological disease representing these diseases with emphasis on their effect on women and there is, by necessity, some overlap between this and the previous section. As a non-American, I would feel more comfortable to believe that the high number of female patients with peripheral nerve injuries secondary to physical beatings, knife wounds, or gunshot wounds reflected the country of origin of this book!

If pushed to criticise, the indexing could be more complete and certain conditions considered in more detail, in particular, paraneoplastic conditions associated with breast and gynaecological malignancies. However, that aside, I think this a rather special book and not only a good addition to any neurological library but a useful purchase for anyone interested in female medical issues.

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The reader may be interested in the following:


### CORRECTION


During the editorial process the descriptions of the histograms in figure 4 (p 614) were wrongly ascribed. The corrected figure is reproduced below.

![Figure 4 Correlation of clinical response](http://jnnp.bmj.com/Downloadedfrom)
Repetitive transcranial magnetic stimulation in the treatment of chronic negative schizophrenia: a pilot study

E COHEN, M BERNARDO, J MASANA, F J ARRUFAT, V NAVARRO, J VALLS-SOLÉ, T BOGET, N BARRANTES, S CATARINEU, M FONT and F J LOMENA

J Neurol Neurosurg Psychiatry 1999 67: 129-130
doi: 10.1136/jnnp.67.1.129