LETTERS TO THE EDITOR

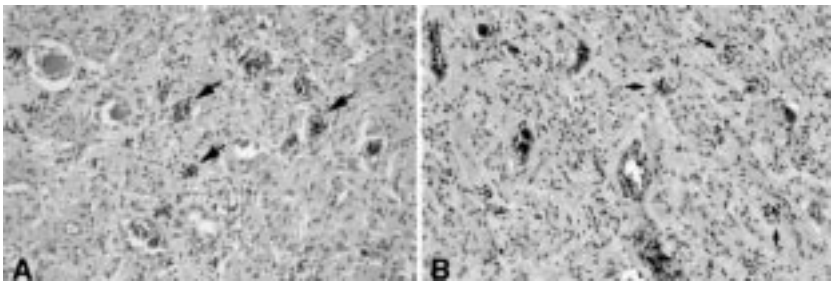
Subacute autonomic and sensory ganglionopathy: a postmortem case

Acute autonomic and sensory neuropathy (AASN) is characterised by severe autonomic dysfunction, sensory deficit, and relatively well or fully preserved motor nerve function.[1–4] The disease sometimes has a chronic course.[2 4] Detailed information is limited because there have been so few reports of the postmortem examination of AASN.[2–4] This case provides histopathological evidence for autonomic and sensory ganglionopathy in AASN.

A 30 year old Japanese man had abdominal pain and a rise in body temperature to 40°C on 1 January 1990. On 23 January, he felt prickling and paraesthesia in all his limbs. On 14 February he could no longer walk due to severe prickling of the entire body. On 2 March, he became bedridden because of orthostatic hypotension. He experienced mild weakness in the all limbs, dysarthria, and dysphagia. On 13 March, he was transferred to our hospital. Physical examination on admission showed anhidrosis, urinary retention, hyposalivation, and paralytic ileus. There was no history of intoxication by drugs or food preceding the illness. His blood pressure was 122/70 mm Hg when supine and 80/46 mm Hg when sitting with no increase in heart rate. His skin was dry. Neurologically, the right pupil was round and 5.5 mm in diameter, whereas the left was oval shaped and 6.0 mm in diameter. The light reflex was sluggish, and the convergence reflex absent bilaterally. Muscle power was mildly weak in his limbs, and there was moderate limb ataxia. Deep tendon reflexes were decreased. Sensation was lost to all modalities over his entire body, including the face. Complete blood cell and serum biochemistry findings were normal. Epstein-Barr virus antibody titres were not raised in the serum. His CSF was normal. Motor conduction velocities (MCVs) and compound motor action potentials were normal in the right median nerve and the right tibial nerve. No sensory nerve action potentials (SNAPs) were evoked in the bilateral sural nerves. The coefficient of variation of the R-R interval on his ECG was reduced (1.9%). In October, dysarthria, dysphagia, and muscle weakness gradually lessened. Despite the improvement in muscle power, severe sensory impairment and paraesthesia of the entire body, as well as orthostatic hypotension persisted. His response to plasmapheresis and high dose corticosteroids was very poor. Two years later, at the age of 33, he died of heart failure.

No tumour was found on general pathological postmortem examination. The dorsal fasciculus at all levels of the spinal cord showed an almost complete loss of myelinated fibres, and the number of dorsal horn cells were decreased. Both the gracilis and cuneatus neurons of the medulla oblongata were slightly decreased. The dorsal roots were atrophic. No detectable changes could be seen in the lateral and ventral fasciculus; nor any clear reduction in the number of neurons in the ventral or lateral horn at Th4 levels. In the cervical (figure A), thoracic, and lumbar dorsal root ganglia, only a few neurons could be seen under low power, with Nageotte nodule formation. In the cervical (figure B) and lumbar sympathetic ganglia, the number of neurons were severely reduced without lymphocyte infiltration. Examination of the dorsal root showed severe loss of myelinated fibres, whereas the ventral root of L3 appeared normal.

This case seemed to be compatible with AASN. Parasympathetic failure was reflected in the loss of salivation, decreased intestinal peristalsis, and bladder atony. Absence of sweating, orthostatic hypotension, and slowness of pupillary dilatation indicated sympathetic failure. Sensory neuropathy was confirmed by an electrophysiological study. The absence of SNAPs in the normal MCVs is best explained by selective involvement of the neurons in lumbar dorsal root ganglia. Neuropathologically, there were no changes in the lumbar ventral roots, but there was severe loss of myelinated fibre in the dorsal roots. Severe degeneration was found in the lumbar dorsal root ganglia neurons at all levels. The slight decrease in the gracilis and cuneatus neurons in the medulla oblongata is thought to be due to anterograde transsynaptic degeneration, as is the slight decrease in the number of dorsal horn cells. As judged by the pathological findings, the site of the sensory nervous system lesion in this case was the lumbar dorsal root ganglia. Similar severe degeneration was found in the sympathetic ganglion neurons, but neurons in the lateral horn remained intact. The site of the autonomic nervous system lesion in our case, therefore, is considered in the sympathetic ganglion. Our case showed the same degree of neuropathologically severe autonomic and sensory ganglinopathy. There have been a few postmortem records of AASN.[2–4] Fagius *et al*[2] showed that the main lesions were in the dorsal root ganglia, dorsal roots, and posterior columns, but they did not examine the autonomic neurons. They speculated that the main lesion responsible for autonomic symptoms was in peripheral nerves. Tohgi *et al*[4] reported severe pathological changes in preganglionic and postganglionic neurons of the autonomic nervous system, posterior columns, and the peripheral nerves, but there they did not describe any pathological findings for the lumbar dorsal root ganglia. Thus they suggested that the main lesion of sensory symptoms was in the peripheral nerves judging from sural nerve biopsy. One report showing both autonomic and sensory ganglion involvement was by Stoll *et al*,[3] who described a 68 year old man with AASN. He died of sudden cardiac arrest four months after onset. In contrast with our case, their patient showed rapid onset (two days) and a very good response to corticosteroids. A postmortem examination detected numerous lymphocytic infiltrates and degeneration in the autonomic and sensory ganglia and, to a lesser extent, in the dorsal roots, dorsal columns, and brainstem. Thus their case is similar to ours in neuropathological lesions. Despite the differences in response to therapy, inflammatory change, and disease course between their patient and ours the pathological findings indicate that the disease, selectively involving both autonomic and sensory systems, is ganglionopathy, not neuropathy.



(A) Section from the lumbar dorsal root ganglia: There are only a few normal lumbar dorsal root ganglia neurons. (B) Section from the sympathetic ganglion: normal nerve cell bodies have disappeared and been replaced by clusters of cells ("nodules of Nageotte" (arrows)). Originally×100.

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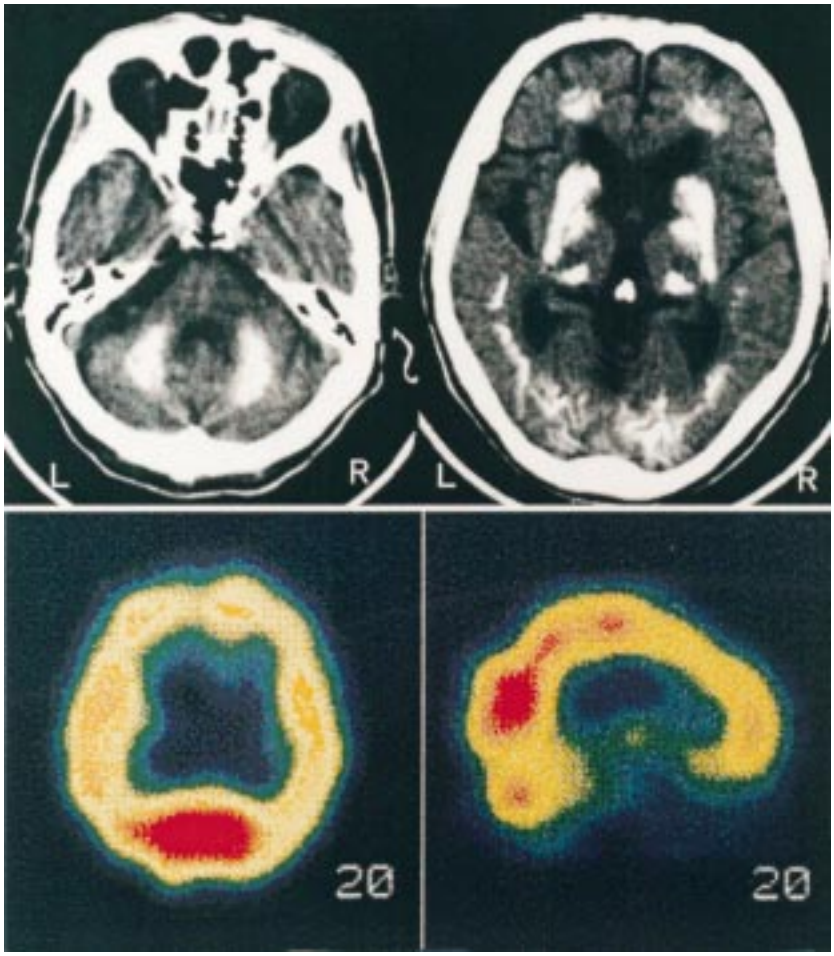
Intracranial calcification with IgG λ M-proteinaemia: a case report

Recently Kosaka reviewed 16 cases of slowly progressive presenile cortical dementia thought to be a clinicopathological entity with pathological features characterised by circumscribed lobar atrophy, diffuse neurofibrillary tangles, and calcification of the Fahr type and named diffuse neurofibrillary tangles with

calcification.[1] However, the pathogenesis and biochemical findings of this new entity are not known in detail. Herein, we report on a patient with presenile dementia, intracranial calcification, and M-proteinaemia, which may play some part in the development of intracranial calcification with dementia.

A 66 year old man was admitted with dementia, which had been apparent since about 60 years of age. At the age of 62 he started to lose spontaneity and at the age of 66 gait disturbance occurred. In addition he showed slurred dysarthria, mild muscle rigidity, bilateral pyramidal signs, and mild truncal ataxia. Dementia slowly progressed and his dementia scales were as follows. Hasegawa's dementia rating scale revised was 16/30 points, mini mental state examination was 20/30 points, the Japanese Wechsler adult intelligence scale revised showed verbal IQ 83, performance IQ 67, and total IQ 74. His routine laboratory investigations were normal. In particular, serum calcium and phosphorus were within the normal range. Twenty four hour urinary calcium and phosphorus were also within the normal range. Serum pyruvate, lactate, vitamins, including 1.25-(OH)2-vitamin D, and analysis of amino acids were within normal limits. Wasserman's test, rheumatoid arthritis test, antinuclear antibodies, and DNA antibodies were all non-reactive. Endocrinological tests showed a slightly low concentration of parathyroid hormone (173 pg/ml; normal range 180–560 pg/ml), other tests, including the Ellsworth Howard test and thyroid function, gave normal results. Immunoelectrophoresis showed the presence of IgG λ M-protein in serum. Bence-Jones protein was not detected in urine. Routine CSF tests were normal for cell counts and protein concentrations. The concentrations of amyloid β (Aβ) 1–40 and Aβ1–42 in CSF measured by enzyme linked immunosorbent assay (ELISA)[2] were 1659 fmol/ml and 179.1 fmol/ml respectively, which were within the normal ranges. The concentration of tau protein in CSF measured by a sandwich ELISA (Innogenetics, Belgium) was raised at 457 pg/ml. Bone marrow was normal. Chest radiography and CT showed calcification of the aorta, pleura, pericardium, and diaphragm. Brain CT and MRI (figure) disclosed calcification in the basal ganglia, the floor of the cortices, subcortical white matter, and cerebellum. Magnetic resonance angiography showed no evidence of arteriosclerosis. The cerebral blood flow measured by ^{123}I-IMP SPECT showed hypoperfusion in the frontotemporal lobes (figure). Neurophysiological tests including auditory brainstem responses, sensory evoked potentials, and peripheral nerve conduction velocities were normal.

Diffuse neurofibrillary tangles with calcification is a presenile dementia as proposed by Kosaka[1] and its clinical characteristics are (*a*) presenile onset, (*b*) slowly progressive cortical dementia, (*c*) more common temporofrontal focal signs rather than parietooccipital signs, (*d*) atrophy of the frontotemporal lobes on CT or MRI, (*e*) calcification of the bilateral globus pallidus and dentate nucleus, (*f*) hypoperfusion in the frontotemporal lobes on SPECT or PET, (*g*) normal serum calcium and phosphorus concentrations .



Plain brain CT and ^{123}I-IMP SPECT. Brain CT showed severe calcification in the basal ganglia, floor of cerebral cortices, subcortical white matter, and cerebellum. ^{123}I-IMP SPECT showed hypoperfusion in the frontotemporal lobes.

Our present case showed presenile slowly progressive cortical dementia and loss of spontaneity. Brain CT and MRI disclosed symmetric non-arteriosclerotic, intracranial severe calcification. Although parathyroid hormone was slightly low, other hormones measured and serum calcium and phosphorus were within normal limits, suggesting that intracranial calcification was idiopathic. The CSF study of Aβ and tau protein is considered a biological diagnostic marker for Alzheimer's disease.[3–5] Decreased Aβ1–42 and increased tau protein are specific for diagnosis of Alzheimer's disease. The CSF concentration of Aβ1–42 was within the normal range and the CSF concentration of tau protein was high which may indicate the absence of deficits in Aβ metabolism but the presence of neurofibrillary tangles. Besides, our patient had IgG λ M-proteinaemia without Bence-Jones protein. The study of bone marrow indicated no malignancy. The gammopathy was considered to be monoclonal gammopathy with undetermined significance. Previously Nishiyama *et al*[6] reported a 41 year old woman with idiopathic intracranial calcification associated with M-proteinaemia, followed by multiple myeloma. Her symptoms were dystonia, gait and speech disturbance, and dementia. This case suggested an association between M proteinaemia and dementia with intracranial calcification. Tentolouris *et al*[7] reported three cases of familial calcification of the aorta and calcific aortic valve disease associated with a monoclonal λ-chain gammopathy. They indicated that immunological abnormalities were associated with calcifications, but they did not assess the CNS.

Without the pathological evidence, clinically this case appeared to be consistent with the criteria for diffuse neurofibrillary tangles with calcification and CSF studies may indicated the presence of neurofibrillary tangles. At present, little is known about the biological and pathogenetic findings in diffuse neurofibrillary tangles with calcification. The present case suggests that M-proteinaemia may play a part in the development of dementia with intracranial calcification such as diffuse neurofibrillary tangles with calcification. Further biochemical studies are necessary in patients with dementia and intracranial calcifications.

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Subacute combined degeneration of the spinal cord after nitrous oxide anaesthesia: role of magnetic resonance imaging

Among all the possible causes of myelopathy, subacute combined degeneration of the spinal cord, neurological complication of vitamin B12 (cobalamin) deficiency, is one of the less often seen.

We report a case of subacute combined degeneration of the spinal cord occurring postoperatively after nitrous oxide anaesthesia in a patient previously undiagnosed to be vitamin B12 deficient.

A 73 year old woman underwent surgery for knee prothesis; forty days later she suffered a femoral fracture due to an accidental fall. Two weeks after surgical stabilisation performed under general anaesthesia with nitrous oxide, the patient complained of gradual onset of loss of gait and weakness of the upper limbs associated with hypoaesthesia of her hands and feet. Neurological deficits progressively worsened so that the patient was admitted to the hospital with severe tetraparesis with bowel and bladder dysfunction. Neurological examination disclosed paraplegia with pronounced loss of strength of the arms, generalised hyporeflexia, and loss of vibration sense; cranial nerves were normal, mental signs were not evident. Magnetic resonance imaging (1.0 T) of the cervicothoracic spine disclosed considerable cord swelling; no abnormalities of signal intensity in T1 weighted sagittal images were evident, whereas abnormally increased signal intensity lesions were detected in T2 weighted images in the posterior cord (figure, A) involving, to a lesser degree, also the lateral columns (figure, C). Brain MRI was unremarkable. Laboratory studies showed macrocytic (mean corpuscolar volume 110 fl, normal 82 to 96 fl; packed cell volume 38%) anaemia (12 g/dl), low concentrations of iron (16 μg/dl, normal 37–145 μg/dl), and vitamin B12 (53 pg/ml, normal>200 pg/ml); folate was within normal values.

Gastric endoscopy disclosed the presence of chronic atrophic gastritis. Iliac crest biopsy showed a hypercellular bone marrow with an appreciable number of megaloblastic forms.

Diagnosis of subacute combined degeneration of the spinal cord was established. Treatment with cobalamin was immediately started (1 mg intramuscularly daily for seven days and thereafter once monthly), with continuous and progressive improvement; vitamin B12 values became normal in two weeks and remained stable. At eight month follow up the patient was able to stand up and walk unassisted; strength was normal in the upper limbs whereas hypoaesthesia with impairment of vibratory sense, even if improved, persisted altered in four limbs. Magnetic resonance imaging showed considerable improvement of previous abnormalities, only faint hyperintensities in the posterior columns of the cervical spinal cord persisting; cord swelling was no longer detected (figure, B, D).

Pernicious anaemia is the most common cause of vitamin B12 deficiency. The spinal cord is usually affected first by vitamin B12 deficiency and often exclusively.

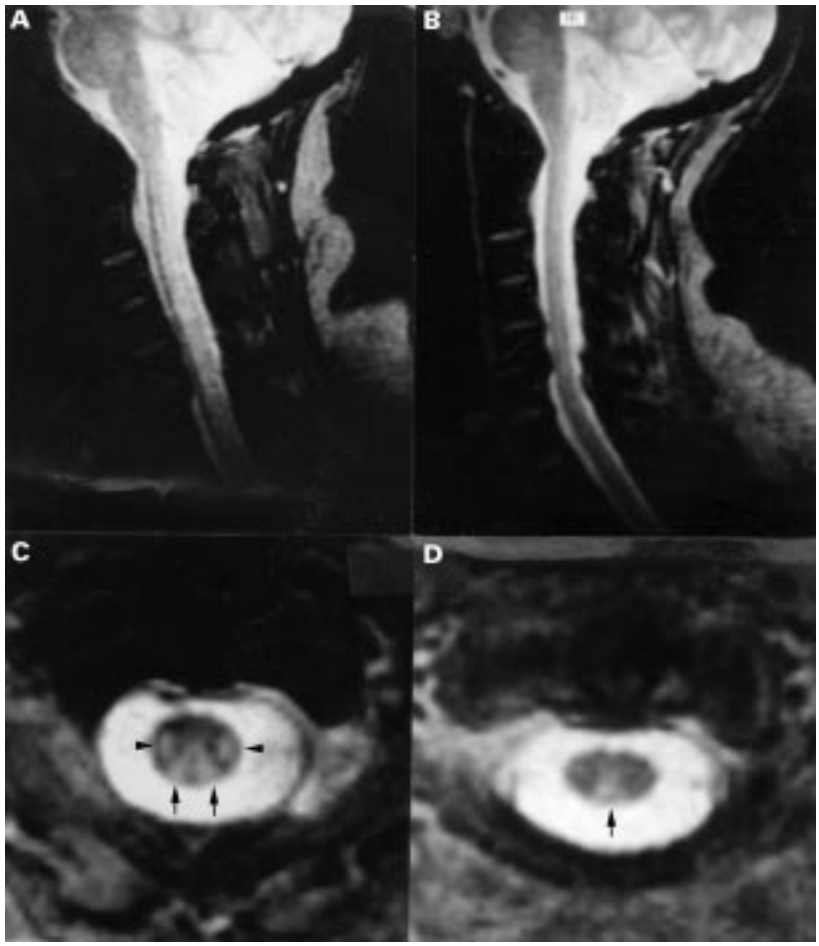
Neurological dysfunctions are due to progressive demyelination, sometimes followed by axonal loss, which starts in the posterior columns and spreads anteriorly involving the lateral and anterior columns; the process begins in the lower cervical and upper thoracic cord, spreading up and down the cord as well. The same neuropathological pattern can be found also in peripheral and optic nerves and, more rarely, in the white matter of the brain.[1 2]

The progression of pathological changes in the spinal cord is reflected in the course of the disease; this results in a clinical picture consisting of the association of myelopathy and polyneuropathy.

Mental signs are frequent, ranging from irritability, apathy, somnolence, suspiciousness, and emotional instability to a pronounced confusional or depressive psychosis with intellectual deterioration. Replacement therapy with cobalamin is usually followed by almost complete resolution of symptoms.

Demyelination is disclosed at MRI as high signal intensity lesions on T2 weighted images, explained by increased water content.[2] A slight degree of expansion was seldom noted.[3] Pronounced, multifocal contrast enhancement of the cervical and thoracic sections of the spinal cord after administration of gadolinium DTPA, indicating blood-CNS barrier disruption, was recently reported.[3] Even if involvement of posterior columns is the origin of a characteristic MRI pattern, it is important to notice that similar findings can be found also in cases of purely spinal forms of multiple sclerosis, combined system disease of non-pernicious anaemia type, peripheral neuropathy (as in POEMS syndrome), and other rare pathological conditions.

Our patient, not known as vitamin B12 deficient, developed subacute combined



GE T2 weighted images of the cervical spine in the midsagittal (380/18/18:TR/TE/FA) and axial (510/15/15:TR/TE/FA) planes at the level of C2 at admission (A, C) and 8 months later after replacement therapy with cobalamin (B, D). At admission cord swelling is evident;high intensity lesions involve the posterior (C, arrows), and to a lesser degree, also the lateral (C, arrowheads) columns of the entire cervical spinal cord. Control examination shows the persistence of only faint hyperintensities in the posterior columns (D, arrow); the volume of the spinal cord is normal.

degeneration of the spinal cord two weeks after nitrous oxide anaesthesia given during surgery for stabilisation of a femoral fracture.

At the present time there is growing acceptance that the clinical picture of neurological dysfunction due to contact with nitrous oxide takes the form of vitamin B12 deficiency. This finding is supported by a sizeable body of laboratory investigations indicating that nitrous oxide exerts its biological effects exclusively through interference with vitamin B12, necessary for DNA synthesis and for the maintenance of myelin sheaths.[4]

The neurological effects of long term nitrous oxide exposure were first reported in 1978 in several people who used nitrous oxide for recreational purpose.[4 5] A neurological syndrome identical to that of vitamin B12 deficiency was noted.[6]

Whereas short term nitrous oxide exposure in healthy people seems to have no appreciable sequelae, the administration of nitrous oxide anaesthesia in patients with unsuspected vitamin B12 deficiency can induce neurological changes, highlighting a previous subclinical condition.

Preoperative vitamin B12 concentrations should be obtained in patients with increased mean corpuscular volume indexes, or affected with gastric mucosa atrophy or previous gastric or intestinal resections. In this way vitamin B12 deficiency would be easily corrected before and after anaesthesia and surgery to avoid possible neurological complications.

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Acute polyneuropathy with chronic lymphocytic leukaemia and paraproteinaemia: response to chlorambucil and prednisolone

Paraproteinaemic polyneuropathies are usually chronic and respond poorly to treatment.[1] An exception to this is seen in the POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes),[2] in which polyneuropathy may improve after treatment for the osteosclerotic myeloma with which it is often associated. Progressive paraproteinaemic neuropathies may also be associated with multiple myeloma, Waldenstrom's macroglobulinaemia, monoclonal gammopathy of undetermined significance, amyloidosis, and Castleman's disease.[3] Monoclonal gammopathy is often detected in patients with chronic lymphocytic leukaemia,[4] but the association between paraproteinaemic polyneuropathy and chronic lymphocytic leukaemia has not previously been reported.

A 73 year old woman with diet controlled diabetes developed, over three days, progressive, bilateral leg weakness without sensory disturbance or sphincter symptoms. Examination disclosed a profound flaccid leg weakness with areflexia and flexor plantar responses. There was a partial right third cranial nerve palsy and poor adduction of the left eye, which improved spontaneously within two weeks of admission. The spleen tip was palpable, but there was no hepatomegaly or lymphadenopathy. Investigations included a white blood cell count of 160×10^9/l, platelets 90×10^9/l with normal haemoglobin, electrolytes, and liver function. An IgG κ-paraprotein band (33 g/l) was detected on protein electrophoresis. Morphology and immunophenotyping of the white cells in peripheral blood and bone marrow were diagnostic of chronic lymphocytic leukaemia. MRI of the brain and thoracolumbar spine was normal. Total protein in CSF was 1.3 g/l (normal 0.3–0.6 g/l) and glucose was 3.4 mmol/l (plasma 4.7 mmol/l). No atypical lymphocytes were seen on a centrifuged specimen. Nerve conduction studies performed 10 days after admission showed absent sural nerve sensory action potential and distal slowing of motor conduction in both upper and lower limbs (ulnar nerve distal motor latency 4.7 ms and conduction velocity 46 m/s; common peroneal nerve distal motor latency 8.5 ms and conduction velocity 34 m/s). Ulnar nerve F response was 33.6 ms and no F responses were detected from common peroneal nerve stimulation. No antibodies against myelin associated glycoprotein were detected in the serum. A diagnosis of postinfectious acute inflammatory demyelinating polyradiculopathy (AIDP) prompted treatment with intravenous immunoglobulin. After six weeks without improvement treatment with 60 mg prednisolone daily was started. A sural nerve biopsy showed severe loss of large and small myelinated fibres, but no malignant infiltration or deposition of amyloid light chains or cryoglobulin. After 10 weeks without clinical improvement and still wheelchair bound, treatment with 10 mg chlorambucil daily was started. Within a week of this treatment she could lift her legs off the bed. After six cycles of combined treatment (two weeks 10 mg chlorambucil, 40 mg prednisolone daily, followed by two weeks off treatment) she was able to walk with a stick. Her white cell count had fallen to 8×10^9/l (46% lymphocytes) and her paraprotein to 8 g/l.

Chronic lymphocytic leukaemia is the most common human leukaemia but infrequently causes neurological symptoms. The predominant neurological complications of chronic lymphocytic leukaemia are due to meningeal[5] or peripheral nerve infiltration,[6] both of which were excluded in our patient. Although rare cases of axonal peripheral neuropathy have been described in patients with chronic lymphocytic leukaemia,[6] we think that this is the first case of a paraproteinaemic demyelinating polyneuropathy associated with chronic lymphocytic leukaemia. This case is not typical of the POEMS syndrome in that the neuropathy was of relatively acute onset, there was no endocrinopathy or skin changes and, in POEMS, the underlying haematological disorder is usually osteosclerotic myeloma. An autoimmune aetiology of the polyneuropathy seems likely as quantitative defects of the immunoglobulins in chronic lymphocytic leukaemia can disrupt the anti-idiotype network's regulation, resulting in autoimmune manifestations that may affect peripheral nerves. In addition, peripheral demyelination may be caused by binding of the paraprotein and complement C3b to myelin associated glycoproteins.[7] It is of interest that specific treatment of the lymphoproliferative condition in our patient resulted in a reduction in the paraprotein and a dramatic clinical improvement.

This case emphasises the diversity of haematological malignancies that can manifest as paraproteinaemic demyelinating polyneuropathy. The prognosis for neuropathies associated with paraproteinaemia is generally poor, but this case suggests that chronic lymphocytic leukaemia, in addition to POEMS, is an example in which treatment of the underlying disorder may modify the natural history of the neuropathy.

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Endovascular electroencephalography during an intracarotid amobarbital test with simultaneous recordings from 16 electrodes

Recently, Boniface and Antoun[1] reported endovascular EEG during intra-arterial amobarbital tests using an endovascular guide wire as the different electrode for bipolar recordings against an extracranial surface electrode (T3) or an average reference. They concluded that their technique was feasible to identify intracranial epileptiform discharges and was less invasive than other intracranial EEG methods with the advantage that it was possible to move the guide wire between different intracranial sides. They also mentioned "the potential to achieve more in a bipolar format when the electrical characteristics of the electrode are optimised".

Our experience with this technique[2] prompted us to use a multilead catheter developed for cardiological examinations (PathfinderTM, Cardima, 47201 Lakeview Boulevard, Fremont, CA 94538, USA) with eight pairs of electrodes (electrode length 0.5 mm, interelectrode spacing 2 mm; electrode pair spacing 6 mm). This allows bipolar recording simultaneously from each electrode to an extracranial surface electrode (FZ) (figure). Our endovascular EEG shows pulse artefacts in some leads, which are a common problem of this technique,[1–3] but they were less pronounced than other recordings.[1] Using the tip of the guide wire as the different electrode, as done by previous groups,[1–3] has the disadvantage that recordings are achieved from a single area at one time only and that the guide wire has to be moved to record from other parts of the temporal lobe. The catheter we used, however, provides simultaneous recordings from 16 different points over a length of 72 mm of the temporal lobe. Such a technique may be of interest during pharmacological activation of epileptogenic foci with short acting barbiturates,[4] and especially during the intracarotid amobarbital test, as this test is routinely performed during presurgical evaluation of patients with medically intractable temporal lobe epilepsy and is known to activate the epileptic focus in more than half of the patients.[5] The clinical use of this technique awaits further evaluation in an appropriate number of patients.

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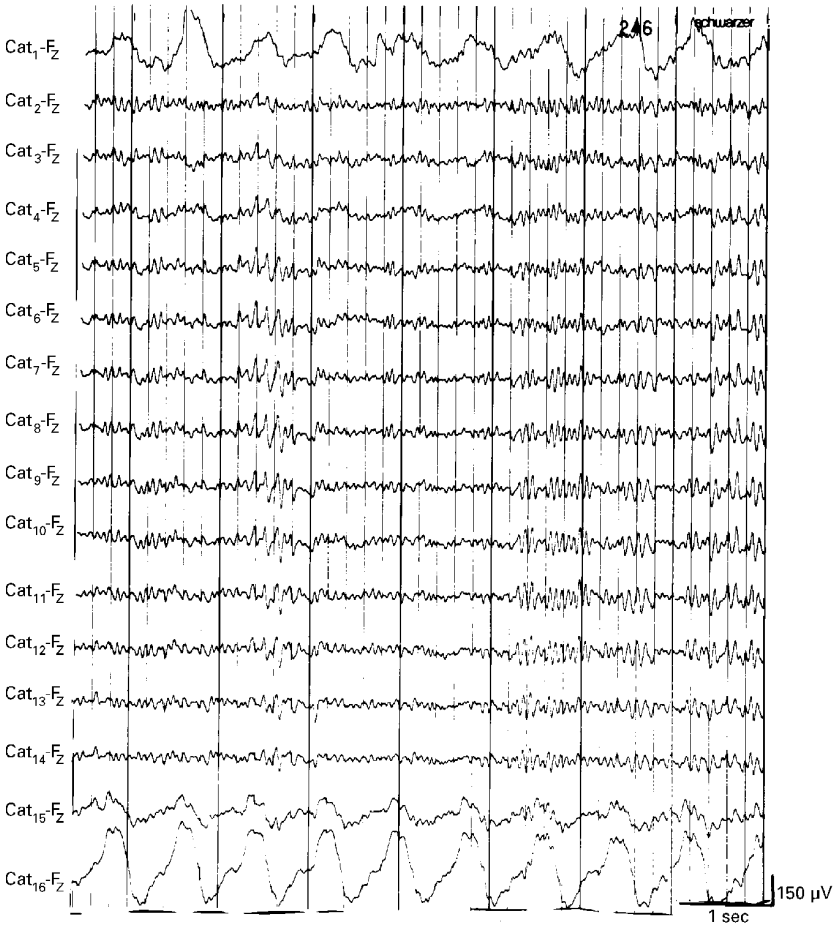

Endovascular EEG using a catheter with 16 electrodes. Bipolar recording between every single electrode and an extracranial surface electrode at FZ. (The electrodes were placed one after another over a length of 72 mm, Cat1 refers to the distal electrode at the tip of the catheter and Cat16 to the proximal electrode at the end of the line of electrodes.)

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2 Stoeter P, Dieterle L, Meyer A, *et al*. Intracranial electroencephalographic and evoked-potential recordings from intravascular guide wires. *Am J Neuroradiol* 1995;**16**:1214–7.
3 Zeitlhofer J, Feldner G, Heimberger K, *et al*. Transarterielles EEG bei superselektiver zerebraler Angiographie. *Zeitschrift für Electroenzephalography Electromyographie und vervandte Gebiete* 1990;**21**:70–2.
4 Aasly J, Blom S, Silfvenius H, *et al*. Effects of amobarbital and methohexital on epileptic activity in mesial temporal structures in epileptic patients. An EEG study with depth electrodes. *Acta Neurol Scand* 1984;**70**:423–31.
5 Hufnagel A, Elger CE, Baker DK, *et al*. Activation of the epileptic focus during intracarotid amobarbital test. Electrocorticographic registration via subdural electrodes. *Electroenceph Clin Neurophysiol* 1990;**75**:453–63.

Standardising care and clinical trials

In his editorial on the Brain Trauma Foundation guidelines for the management of severe head injury, Kirkpatrick argues that standardisation of care is a prerequisite for the conduct of multicentre randomised trials.[1] A similar concern seems to have motivated the European Brain Injury Consortium to develop its "expert opinion" based guidelines.[2] This is not the case. Providing that a trial is large enough, randomisation will ensure that the intervention and control groups are identical with regard to known and unknown confounders. It is conceivable that the size of the intervention effect may vary a little depending on the other aspects of care given, but not the direction of the effect. Patients in the future will almost certainly receive different forms of care than they do today, and treatments shown to be effective today may be more or less effective in the future, but the direction of the effect will be the same. Rather than standardise care, it would be more useful to make sure that clinical trials were large enough to detect reliably moderate but clinically important treatment effects. Even though thousands of patients each year are treated with hyperventilation, barbiturates, mannitol, and steroids, clinical trials of these interventions, even in aggregate, have involved less than a few thousand patients, and for hyperventilation, mannitol, and barbiturates, existing trials comprise less than a few hundred patients. It is not surprising that the Brain Trauma Foundation was unable to define evidence based standards of care.

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1 Kirkpatrick PJ. On guidelines for the management of the severe head injury. *J Neurol Neurosurg Psychiatry* 1997;**62**:109–11.
2 Mass AI, Dearden M, Teasdale GM, *et al*, on behalf of the European Brain Injury Consortium. EBIC-Guidelines for management of severe head injury in adults. *Acta Neurochir* 1997;**139**:286–94.

Kirkpatrick and Pickard reply:

We are grateful for the letter from Roberts which highlights the concept that randomised controlled trials can detect small treatment benefits provided such trials are large enough. Although correct in theory, this concept still assumes that the pathology treated shows some degree of homogeneity. It is now becoming clear that the number of known and unknown confounding variables with acute brain injury dramatically increases the number of patients required to prove efficacy. At some point this number exceeds that which is practicable and affordable, especially as the regulatory authorities demand that pharmaceutical phase III trials collect vast and expensive data sets. The randomised controlled trials which have shown treatment efficacy (for example, streptokinase for acute mycocardial infarction, aspirin and dipyridamole for the prevention of stroke and myocardial infarction, nimodipine for subarachnoid haemorrhage, and carotid endarterectomy for stroke prevention) have considered conditions with well defined end points sharing common pathological mechanisms. Head injury does not fall into this stereotype in view of the multiple interacting and opposing pathological mechanisms and the range of possible outcomes which are difficult to quantify.

Confounding variables influence outcome in particular conditions to different degrees. Attention to blood pressure, fluid balance, and systemic oxygenation may have only a modest influence on outcome after myocardial infarction, but are known to have a profound influence on the victim of brain injury. A specific treatment may have variable effects on different pathophysiological events operating within the same condition. Thus hyperventilating a patient with head injury with associated cerebral oligaemia is likely to be harmful, whereas this approach for raised intracranial pressure due to hyperaemia is more appropriate. By contrast the use of mannitol (which increases cerebral blood flow), may be beneficial for the first, but potentially harmful for the second. Hence the effect of a given intervention is not a simple matter of magnitude as suggested by Roberts, as the direction of the effect may differ in different subgroups.

Retrospective analysis of subgroups in phase III randomised control trials to correct for such imbalances have been received rightly with scepticism, but such an exercise can be used to direct the design of future trials to reduce the "noise" in the system. The suggestion that head injury subgroups be identified and a more stable physiological background be provided, is not dissimilar to that adopted for the randomised control trials of carotid endarterectomy, in which subpopulations were defined according to the grade of stenosis and the presenting symptom stereotype. If this had not been done, the efficacy would have been diluted to extinction.

The purpose of publishing standards of care in the head injury environment is largely educational, highlighting the lack of definitive evidence and the difficulty in obtaining it. None the less, ironing out key important variables will help to generate a substrate for testing intervention on defined subpopulations which share common pathology. Even if the standard proves to be harmful, delivery to the test population will provide a more stable pathophysiological baseline and a greater chance of showing individual therapeutic efficacy.

P J KIRKPATRICK
J D PICKARD

BOOK REVIEWS

Head Injury. Physiology and Management of Severe Closed Injury. Edited by PETER REILLY AND ROSS BULLOCK. (Pp 478; £135.00.) Published by Chapman and Hall Medical, London. 1997. ISBN 0-412-58540-5.

For neurosurgeons, head injuries are always with us. They exist like the drones of a bagpipe tune, unchanging in the background while the music goes on elsewhere. This is perhaps why the last major textbook to be published on the subject was that of Jennett and Teasdale in 1981. However, for that small, and diminishing, band of neurosurgical researchers, head injuries provide ideal "case material" for the investigation of new ideas on the ways that insults affect the nervous system and how outcomes might be improved. The fruits of that thinking and investigation are admirably covered in this new book. It represents a tripartite cooperation between those centres in the United Kingdom, Australia, and the United States which have a particular interest in the mechanisms of head injury and management of the patient. Although not all of the content is new, the chapters on the effects of injury at the cellular level represent a particularly useful summary of what has become a very complex pathophysiological process. Similarly the chapters on new methods of investigation in those with head injury, such as PET, SPECT, MR spectroscopy, and transcranial Doppler, represent, for the average neurosurgeon, a useful summary of the applications of new and rapidly developing technologies.

Although promising developments in the field of neuroprotection and perhaps eventually brain repair can be perceived on the distant horizon, of its nature, neuroprotection can at best prevent or minimise secondary damage. To achieve major miracles we will no doubt have to await the more distant promise of brain repair. If such treatments do eventually become available there is no doubt that any such techniques will prove difficult and very expensive. The non-specialist may turn therefore to the regrettably small section on prevention. In the United Kingdom the number of head injuries shows a small but welcome continuing decline, although not all countries are so fortunate. Head injury rates vary widely even in the so called "developed" world. On a recent visit to Amsterdam I was astounded to see, in such a cycle oriented city, not one single rider wearing a protective cycle helmet. Perhaps the time has come to make these compulsory. There is clearly much still to do in the way of head injury protection. Although seatbelts, airbags, and antilock brakes represent good solid progress, considering the remarkable survivals which occur in the high speed crashes in Formula One Grand Prix motor racing, there is clearly a lot more which could be achieved given the potential will and the financial investment.

The book is a welcome addition to the neurosurgical literature. It is well produced and beautifully presented. Although rather expensive it will no doubt become an indispensable companion for those of us who still have to care for these distressing and still too frequent cases.

DAVID G HARDY

Gait Disorders of Aging. Falls and Therapeutic Strategies. Edited by JOSEPH C MASDEU, LEWIS SUDARSKY, and LESLIE WOLFSON. (Pp 350; £61.00.) Published by Lippincot -Raven, Philadelphia. 1997. ISBN 0-316-54915-0.

Community studies show that around 30% of people aged 65 and over fall each year. Only 10% to 15% of falls result in serious injury but 92% of hip fractures and 96% of wrist fractures in older women are caused by falling. There are important consequences even when no serious physical injury occurs. The anxiety caused by falling can result in loss of confidence and self imposed restrictions on activities, eventually resulting in admission to institutional care.

This book is based on an annual course held at the American Academy of Neurology on gait disorders in elderly people, and the contributors represent some of the participants, including neurologists, geriatricians, physiotherapists, and physiologists. Its stated aim is to be of use to those in clinical practice but also to those planning research.

The book is well structured. It commences with overviews on the physiology of static balance and gait, the effects of aging on them, and clinical research methodology. These are mostly excellent, apart from an overdetailed exposition of the neurophysiology of gait in cats, the relevance of which to two legged humans is difficult to grasp. All the authors are keen to stress the importance of detailed assessment, which is undoubtedly true but becomes rather repetitive.

There follow chapters on a suggested nosology of gait disorders and a clinical approach to diagnosis, both models of clarity and practicality. The detailed discussions of the common underlying diagnoses such as parkinsonism and cerebrovascular disease are generally useful with the exception of that on vestibular and cerebellar disorders. It is abundantly clear which authors deal regularly with older people and which do not, as the latter briefly mention elderly people as a "special group" leaving the reader to wonder whether the rest of the chapter has any relevance to them at all. The final six chapters discuss evaluation and intervention, including risk factor intervention, physical therapy and balance, and resistance training. The chapter on physical therapy is superb, concentrating on a sample case to illustrate how appropriate treatment is planned.

This book usefully brings together a wide and multidisciplinary literature on a complex and fascinating problem. The mistaken assumption that old age itself is a cause of poor balance and falls is still widely held and as a result many professionals display a depressingly defeatist attitude to their management. This book confirms that impaired gait and balance in an older person constitutes a syndrome with a rich differential diagnosis, and that even when a treatable cause cannot be found, much can be done to reduce disability.

NICKI COLLEDGE

Epilepsy and pregnancy. Edited by T TOMSON, L GRAM, M SILLANPAA, AND S I JOHANNESSEN. (Pp 215; £38.00.) Published by Wrightson biomediacal publishing, Petersfield. 1997. ISBN 1 871816 36 X.

The use of antiepileptic drugs in women of childbearing age is one of the most thorny issues regularly facing neurologists. The stakes are high but there is no universally agreed approach to management. This book explores various aspects of the problem, including teratogenicity, epilepsy control in pregnancy, and the consequence of seizures to mother and child in pregnancy and at delivery. There are valuable chapters describing increasing knowledge of the mechanisms of teratogenicity of antiepileptic drugs and the minor developmental and cognitive consequences of anticonvulsant exposure in utero; an area of increasing concern. Breast feeding is also covered. I suspect that most readers would expect to discover a detailed review of current evidence in relation to teratogenicity. This section is really the nub of the book but it lacks sufficiently detailed statistics for a text devoted to this subject and I think that it is just a gateway to the source literature. There are also several key issues in relation to new drugs: how and when they should be used in women of child bearing age; how to manage their pregnancies; and how to coordinate postmarketing surveillance. These matters are not considered; nor is there any information on the most recent antiepileptic drugs, even though some data are available from postmarketing surveillance and from animal studies. This book covers a broad range of issues competently in a series of brief chapters with good literature citations but lacks a sufficiently detailed analysis of teratogenicity of antiepileptic drugs to be of real help to the clinician in making decisions in this potential minefield.

MARK MANFORD

Neurosurgical Aspects of Pregnancy. Neurological Topics Series. Edited by C LOFTUS. (Pp 255.) Published by the American Association of Neurological Surgeons, Park Ridge, ILL. 1996. ISBN 1-879284-36-7.

Pregnancy is a condition encountered infrequently in neurosurgical practice and yet it complicates many facets of patient management, including investigation, drug therapy, anaesthesia, and surgery. As such, clinicians may be unfamiliar with the most appropriate way to manage the condition, nor able to counsel the patient fully as to the precise risk both to the foetus and herself. Although this information is available in the literature it is not readily accessible, particularly in an emergency setting. This book is designed to fill that void by distilling the necessary information into a single slim volume.

This text has been produced by the American Association of Neurological Surgeons as part of its *Neurosurgical Topics* series. It follows the familiar pattern of a review of the literature which is concluded by a short series of multiple choice questions intended as revision for trainees. The book is divided into three parts. The first is a general section which is equally applicable to various disciplines, not just to neurosurgery. It includes the potential foetal toxicity of commonly used drugs, the risks associated with diagnostic imaging and with anaesthesia, haemostatic and thrombotic considerations, and the physiological changes to cardiovascular and cerebrovascular function that occur during pregnancy. The second section covers specific neurosurgical disorders such as back pain, carpal tunnel syndrome, pituitary tumours, subarachnoid haemorrhage, venous thrombosis, benign intracranial hypertension, hydrocephalus, and ventriculoperitoneal shunt management. The final part discusses patient positioning and foetal monitoring for surgery, the intrauterine diagnosis of developmental disorders, the current status of intrauterine surgery, and ethical issues surrounding the management of brainstem death and the permanent vegetative state.

This is a truly excellent volume. All that could be reasonably expected to be covered in a book on this subject is here. The chapters are clear, concise, and have been referenced extensively for further reading. Every practising neurosurgeon should have ready access to this work.

ROBERT MACFARLANE

Handbook of Stroke. Edited by DAVID O WEIBERS, VALERY L FEIGEN, and ROBERT D BROWN. (Pp 450; £34.50.) Published by Lippincot-Raven, Philadelphia. 1997. ISBN 0-316-94760-1.

I approach handbooks with a mixture of eagerness and dread. Some are what they purport to be, fit into the palm and are easy to use in the clinical setting, Others, however, require no little effort to lift and are clearly detailed tomes. This text fits snugly into the white coat pocket of the junior doctor and is comprehensive in its summary of the assessment and treatment of patients presenting with stroke—the authors clearly dislike the overused term "cerebrovascular accident" which they point out contributes nothing to the idea that this is a complex disorder requiring comprehensive appraisal and therapy.

The early chapters provide an extensive guide to the assessment and treatment of the "neurological patient". Smaller sections follow on less obvious subjects such as the telephone assessment of subjects and more detailed differential diagnosis.

Opinions as to the appropriate treatment of cerebral infarction presenting early are evolving rapidly and this text takes an active line, suggesting thrombolytic therapy in line with the certain recent trials and the licensing of tPA for treatment of stroke in the United States.

Rehabilitation becomes the priority in the long term management of the stroke patient and this section is short in comparison with others. By contrast, the appendices provide detailed illustrations, disability scales, risk scales, and algorithms, although colour diagrams could have lifted the illustrations somewhat and some of the assessment forms did not copy well.

Overall, this is an extremely useful tool for the admitting doctor in the assessment and care of the patient with suspected cerebrovascular disease. It should be noted, however, that treatment options suggested are slanted towards practice in the United States making this portion of the book less helpful in the United Kingdom, where practice tends to be more conservative.

Despite this, the publication clearly and concisely fulfills its role as a handbook and should stimulate the physician into further examination of this important subject.

ALASTAIR LANSBURY

Neurologic Disorders in Women. Edited by MERIT E CUDKOWICZ AND MICHAEL C IRIZARRY. (Pp 162.) Published by Butterworth-Heinemann, Oxford. 1997. ISBN 0-–7506–9745–8.

I was a little bemused when first presented with this book, *Neurologic Disorders in Women*. Like many things in life, I suppose I had always accepted that it was more hazardous to be male. After all, are we not always telling men with vascular disease that whereas they can reduce some of their risk factors they can't change being male, or being aware of possible x linked adrenoleukodystrophies in young men with what has been labelled aggressive multiple sclerosis and then there are the x linked muscular dystrophies. So where is the neurological problem in being female? Migraines and epilepsy fluctuate with the menstrual cycle, pregnancy alters the course of multiple sclerosis and the connective tissue diseases, and then there are the potential complications of hormone treatment be it in the shape of the oral contraceptive pill or hormone replacement therapy. And maybe we do have more headaches. But is that really enough on which to base a book? So with these preconceptions I opened the book with curiosity.

Cudkowicz and Irizarry (one woman, one man: an important balance in having such a book accepted) and colleagues from the Massachusetts General Hospital, have divided neurology into nine broad categories including, epilepsy, stroke, headache, and multiple sclerosis. In each chapter a brief overview is provided with particular reference to the incidence and prevalence in females and noting any sex specific features of the disease. Emphasis is then placed on the interaction of the disease with the female functions of menarche, menstruation, menopause, and reproduction including both the hormonal and other aspects of pregnancy, oral contraception and hormone replacement. Much of what is discussed is small print that would be omitted from larger textbooks—for example, that whereas issues surrounding a young woman with multiple sclerosis or a connective tissue related vasculitis who wishes to get pregnant are generally known, what if she had Parkinson's disease or chronic inflammatory demyelinating polyneuropathy or if that same woman wished to breast feed? Such issues are considered. Important pharmacological areas are discussed in detail; the interaction of antiepileptic drugs with other medications, in particular the oral contraceptive pill, the teratogenicity of certain medications, and the role of the oral contraceptive pill and hormone replacement therapy in cerebrovascular disease. The neurological complications, both direct and paraneoplastic, of predominantly female malignancies are also described; a female presenting with a Lambert-Eaton myasthenic syndrome might well have a small cell carcinoma of the lung but could also have a similar carcinoma of the uterus or breast carcinoma and then there is the rare stiff "man" syndrome described in women with breast carcinoma.

So, despite my starting position that there was not such a specific gap in the neurological literature, I have been converted. Perhaps the book should have been named *The Hazards of being a Female with a Neurological Disease* as the strengths of this book lie in describing the role that the menstrual cycle, reproductive functions,and associated factors have in altering the course of a disease or how they alter the therapeutic options. The other great strength of this book is its thorough and up to date referencing. Small and concise, this book will provide an excellent reference source for all physicians treating neurological disorders in women.

GILLIAN HALL

Behavioural Neurology and the Legacy of Norman Geschwind. Edited by STEVEN C SCHACHTER and ORRIN DEVINSKY. (Pp 304; £84.50.) Published by Lippincott-Raven, Philadelphia. 1997. ISBN 0-397-51631-2.

As the title suggests, this edited book is a tribute to the late Norman Geschwind written by 30 or so of his former colleagues and pupils. The first quarter is extremely engrossing and consists of series of short essays dealing with Geschwind as "educator", "advisor", "role model", "teacher", "mentor", etc. The most enduring impression left by this section is what a truly remarkable person he was. I finished many chapters wishing that my exposure had not been limited to hearing a single lecture.

Subsequent sections of the book are more conventional and cover Geschwind's contributions in the areas of language disorders, apraxia, disconnection syndromes, frontal lobe disorders, epilepsy, and aspects of cerebral dominance. Most of the chapters are very well written, although there could perhaps have been a greater editorial input to avoid repetition. For those who have trained more it is salutary to be reminded of the monumental contributions made by this founding father in such a wide range of topics. The book is fitting tribute to a great man. It should be bought by anyone with an interest in the origins and development of behavioural neurology and neuropsychology but the high price is likely to deter a wider readership.

JOHN HODGES

Readers might be interested in the following:

Neuromuscular Diseases During Development. Edited by F CORNELIO, G LANZI, and E FEDRIZZI. (Pp 164; £36.00). Published by John Libbey and Co Ltd, London, 1997. ISBN 0-86196-541-8.

Handbook of Vestibular Rehabilitation. Edited by LINDA M LUXON and ROSALYN A DAVIES. (Pp 160; £24.50). Published by Whurr Publishers Ltd, London 1997. ISBN 1-870332-17-2.

So That Was Life. A Biography of Sir Geoffrey Jefferson. Author; PETER H SCHURR. (Pp 358; £25.00). Published by The Royal Society of Medicine Press Ltd, London, 1997. ISBN 1-85315-305-2.

Atlas of the Human Brain. Edited by JURGEN K MAI, JOSEPH ASSHEUER, and GEORGE PAXINOS. (Pp 328; HB $135.00). Published by Academic Press, San Diego, 1997. ISBN 0-12-465361-8.

Subacute autonomic and sensory ganglionopathy: a postmortem case

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Notes