LETTERS TO THE EDITOR

Volitional and stimulation induced neuromyotonic discharges: unusual electrophysiological pattern in acquired neuromyotonia

Neuromyotonic discharges are electrophysiologically characterised as bursts of motor unit potentials firing at more than 150 Hz for 0.5 to 2 seconds. The amplitude of the response typically wanes. Discharges may occur spontaneously or be initiated by needle movement. Walsh described a case of a mediastinal tumour and neuromyotonia with very high frequency discharges that outlasted voluntary effort.

We report a case of an acquired paraneoplastic neuromyotonia associated with thymoma, clinically manifested myotonia-like muscle stiffness, and an unusual electrophysiological pattern of neuromyotonic discharges that were evoked voluntarily or with electrical stimulation but were absent spontaneously and were not elicited by needle displacement.

A 71 year old women presented with a 6 month history of muscle stiffness, paraesthesia provoked mostly by movement, disturbed speech, and difficult walking. At the time of examination she could not walk independently.

Clinical examination disclosed pronounced dysarthria and ataxic-like limb movement interrupted by superimposed tonic involuntary contractions. The muscle decontraction was prolonged and percussion myotonia was absent. Fasciculations and myokymia-like movements were seen in her legs. A decreased perception of vibration were slightly paretic and atrophic. Tendon myokymia-like movements were seen in her我が家; sensory conduction velocities were borderline.

Nerve conduction studies disclosed bor-

1 mV

Foot switch status: Run

Trig: 100 µV↑

50 ms

Needle EMG from abductor pollicis brevis muscle showing high frequency (about 200 Hz) neuromyotonic discharge with waning amplitude and duration of 250 ms, provoked by voluntary contraction (arrows).

The repetitive motor nerve stimulation study of ulnar and auxiliary nerves performed at a stimulation frequency of 2 Hz showed no decrement.

The complete blockade of ulnar and median nerves at the elbow by lidocaine did not interrupt the ability of shocks delivered distally to the site of the block to evoke neuromyotonic discharges.

The repetitive motor nerve stimulation evoked by electrical stimulation of the motor nerves and the voluntary contraction and the ability to evoke them waned after several contractions they disappeared.

Torbergsen et al stated that, in addition to spontaneous occurrence, neuromyotonic discharges could also be registered during voluntary activation or after nerve stimulation; it was assumed that such a type of electrophysiological abnormality is caused by the slightest degree of hyperexcitability of axons when neuromyotonic discharges are triggered after a preceding impulse, simply voluntary or electrical, has passed, whereas spontaneous neuromyotonic discharges without an obvious trigger are generated in the case of more increased hyperexcitability of axons.

Clinically, as well as muscle stiffness, ataxic-like voluntary movement was present in our patient; this movement was interrupted repeatedly, probably due to repeated bursts of neuromyotonic discharges. Moreover, the movement provoked corresponding sensory phenomena of dysesthesias and paraesthias. It seems likely that these sensory phenomena of dysesthesias and paraesthesiae were evoked by similar types of sensory

improvement; the thymoma was confirmed histologically.

An examination of voltage gated K+ channel (VGKC) antibody titres was performed using immunoprecipitation of ‘T-α dendrotoxin labelled VGKCs extracted from human frontal cortex (Institute of Molecular Medicine, John Radcliffe Hospital, Oxford, UK). The first titre was positive (241 pM (positive titres >200 pM).

During a course of intravenous immunoglo- bulin (IVIg) infusions at a normal dose (0.4 g/kg on 5 subsequent days, total dose of 2 g/kg) both pseudomyotonic and sensory signs and symptoms started to improve and at the end of the IVIg treatment the patient was able to walk independently. After the initial IVIg therapy (administered 1 month before surgical removal of the thymoma), clinical signs and symptoms stabilised with the ability to walk independently for 20 metres. After a year of stabilisation, the stiffness, dysarthria, and walking ability worsened in the course of 3 months to the point at which the patient was once more unable to walk independently.

The patient then received a second course of IVIg therapy (2 g/kg) and improved to the same degree as after the first treatment.

An EMG at the beginning of clinical follow up disclosed sparse fasciculations and myokymic discharges (with a short interburst interval of about 5–10 ms) and motor unit potentials with slightly higher amplitude, longer duration, mild waveform instability, and polyphasic pattern from distal muscles in the lower limbs. Voluntary contraction evoked repetitive bursts of high frequency discharges resembling motor unit potentials with amplitude decrement and a characteristic “pinging” sound (figure); the discharges lasted several hundred milliseconds and were present uniformly in all examined muscles.

The stimulation single fibre EMG from the extensor digitorum communis muscle on the right side showed a slightly abnormal jitter (19 recordings, mean jitter 34 µs, five recordings above 40 µs), which together with a slight increase in fibre density (2.3) indicated the reinnervation process.

Second EMG and conduction studies performed 7 days after the end of the second IVIg treatment showed less frequent neuromyotonic discharges evoked by electrical stimulation of the motor nerves and the voluntary contraction and the ability to evoke them waned; after several contractions they disappeared.

Spa record

Abduc. Pol. Br.L

15:08:25
neural hyperactivity. The high frequency discharges in our patient with neuremyotonia consisted of motor unit potential-like waveforms, which did not arise spontaneously, but the high frequency of about 200 Hz clearly showed their ectopic origin.

We think that actual definitions of neuremyotonic discharges emphasizing their spontaneous occurrence or initiation by needle movement should be reconsidered and modified.

The presence of VGKC antibodies and clinical, immunological, and electrophysiological response to IV Ig treatment are in favor of the role of VGKC blockade in the generation of "evoked" neuremyotonic discharges. Antibodies to VGKC found in our patient may have accessed the paranodal region (due to myelin disturbance in neuremyotrophy) and blocked fast K⁺ channels similarly to 4-aminopyridine. This would enhance supernormality and could thereby allow a single action potential to trigger another discharge or a train to discharge.

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245 C

Polymorphism

ZI*A (G124G), ZI*B (A124G), ZI*C (G245T), and ZI*D (G245T). Here we investigated the association of Parkinson’s disease, pesticide exposure, and these GSTZ1 polymorphisms.

DNA was extracted from blood samples collected from patients with Parkinson’s disease and matched controls as described previously. This study was approved by the Princess Alexandra Hospital ethics committee. Polymorphisms at nucleotide 94 and 124 were detected by polymerase chain reaction/RFLP analysis as described previously. To detect the nucleotide 245 polymorphism, PCR was performed with the following primers: 5’AAGAGGTGTAGTGATGTTGAGTGGC3’ and AAGTGGCC3’. The PCR was carried out in a 20 µl reaction volume containing reaction buffer IV (Advanced Biotechnologies, Epsom UK), 20 mM (NH4)2SO4, 75 mM Tris/HCl pH 9.0, 0.1% Tween 20, dNTPs (0.2 mM), MgCl2 (1.5 mM), primers (0.3 µM each), thermostable DNA polymerase (Advanced Biotechnologies, 0.5 U), and DNA (25 ng). No DNA was added to control reactions. Thermal cycling was carried out using a Corbett capillary thermostable cycler under the following conditions: initial denaturation at 94°C for 2 minutes; subsequently 35 cycles of 94°C for 20 seconds, 60°C for 20 seconds, 72°C for 30 seconds; and a final extension of 72°C for 2 minutes. Products of PCR were digested overnight with restriction enzyme Bsh1236I (MBI fermentas) at 37°C and fragments were separated by 8% polyacrylamide gel electrophoresis and stained with ethidium bromide. The restriction enzyme Bsh1236I cleaves the C245 fragment generating 12, 108, and 142 bp fragments and the T245 fragment generating 108 and 154 bp fragments.

We tested 307 Parkinson’s disease and 105 control populations. The sample populations were in Hardy-Weinberg equilibrium. There were no associations between the nucleotide 245, 94, or 124 polymorphisms and Parkinson’s disease (table). A total of 87 patients and 53 controls reported a history of regular pesticide exposure. In this group there was a weak association between the nucleotide 245 genotype and Parkinson’s disease (p=0.05). Furthermore, in this group, the Z1*C genotype (G124G) was less common in the patients with Parkinson’s disease than in the controls (30% vs 45%; p=0.03, not corrected for multiple comparisons).

There was no overall association between the GSTZ1 polymorphisms and Parkinson’s disease. However, we found a difference when only those who reported pesticide exposure were analysed. We also combined the data for the three polymorphic sites to determine the frequency of the four GSTZ1 alleles. The Z1*C allele is the most common variant in white control populations.

We found that this allele was less common in patients with Parkinson’s disease than controls when stratified for pesticide exposure. Studies of this nature have limitations related to selection bias, case ascertainment, recall bias, difficulty in assessing exposure, and multiple comparisons. Accordingly, our conclusion that there is a potential association between GSTZ1, pesticide exposure, and Parkinson’s disease must be considered preliminary. Nevertheless, it is interesting that there have now been several reports suggesting an association between the risk of Parkinson’s disease, polymorphic variability in detoxification genes, and exposure to environmental toxins. These include CYP2D6 and solvent exposure, GSTP1 and pesticide exposure, and CYP2D6, pesticide exposure, and Parkinson’s disease with dementia. Thus, it has been recognised that studies examining the association of polymorphic variation in xenobiotic metabolism genes and Parkinson’s disease should take into account the effect of exposure to toxins.

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A case of stiff limb syndrome responsive to plasma exchange

Stiff limb syndrome is a rarely described, rare condition that is characterised by rigidity within the limbs that progresses in a relapsing and remitting fashion, often with involvement of the sphincters and brain stem. The axial muscles are spared in the early stages of the illness, which helps distinguish it from stiff man syndrome, although it may still represent a similar pathogenic mechanism to that
proposed in stiff man syndrome, in which anti-GAD antibodies are typically seen in at least 60% of patients. However, patients with stiff limb syndrome seem to have different neurophysiological abnormalities from stiff man syndrome and fewer of these patients have anti-GAD antibodies; they also typically show a poorly sustained response to baclofen and diazepam. The response to immunotherapy in stiff limb syndrome is not known, whereas patients with stiff man syndrome may respond to intravenous immunoglobulin as well as possibly plasma exchange. We now report on a patient with stiff limb syndrome who responded dramatically to plasma exchange and in whom an abnormality was found, suggesting that this condition may have an immunological basis.

A 50 year old retired auxiliary nurse presented with a 10 year history of progressive pain, stiffness, and flexion contractions in her hands, followed by increased immobility. Her neurological problems began at 24 years of age when she developed viral meningitis based on a headache, fever, and a CSF lymphocytosis resolved within a week. At the age of 28 she complained of back and leg pain with urinary retention but displayed no abnormal neurological signs and had a myelogram that was normal. Her leg symptoms remained, she continued to complain of urinary retention and frequency, for which no cause was found. She went on to have a urethrotomy which did not relieve her symptoms. At the age of 40 she started to develop stiffness in the hands, which slowly clawed, after which her arms and neck became progressively stiffer and her trunk became increasingly stooped on walking, with additional difficulty raising her arms above her head. Five years after the onset of her symptoms she was incapacitated, required assistance with all activities of daily living, and was permanently catheterised. At this stage a seronegative polyarthritis was diagnosed and she was treated with hydroxychloroquine, prothiaden, and corticosteroids, all of which showed no effect. On the other hand, patients treated with interferon may develop neurological complications including neuropathy.1 We report the first case of AASN which can be associated with interferon a-2b therapy for chronic hepatitis C.

Acute autonomic and sensory neuropathy after interferon a-2b therapy for chronic hepatitis C

Acute autonomic and sensory neuropathy (AASN) is a disorder characterised by acute autonomic and sensory nerve dysfunctions, and well preserved motor nerve function.1 Although the pathomechanism of AASN is not clear, autonomic and sensory ganglion neuron cell bodies may be the main target of the immune mediated process underlying AASN.2 On the other hand, patients treated with interferon may develop neurological complications including neuropathy.1 We report the first case of AASN which can be associated with interferon a-2b therapy for chronic hepatitis C.

A 57 year old Japanese man with chronic hepatitis C had been treated with interferon a-2b since June 1998. On 3 September, a skin eruption abruptly emerged on his chest and rapidly spread over his whole body. There was no history of exposure to toxins and drugs other than the interferon. The interferon therapy was stopped on 7 September; after a total dose of 390 000 000 units. The skin eruption gradually resolved, but 1 week later, numbness appeared in his limbs. Subsequently he became unable to walk and stand. Further, he developed urinary overflow incontinence and bowel distension. He was then transferred to our neurological department on 2 October.

Physical examination disclosed orthostatic hypotension without secondary tachycardia (120/60 mm Hg lying, 85/52 mm Hg sitting, fixed pulse rate 60 bpm) and paralytic ileus. He was catheterised for incontinence. He was drowsy. The pupils were anisocoric although they reacted promptly to light. Other cranial nerves were unremarkable. Muscle strength and bulk were normal. Deep tendon reflexes were generally absent. There were no pathological reflexes. Light touch, pain, and temperature sensations were impaired moderately over the trunk, more so in his limbs. Vibration and joint sensations were impaired severely in the same distribution, and lost in
his fingers, knees, ankles, and toes. Sensory ataxia and pseudosthesis in his fingers were noted.

Routine laboratory examinations were normal except for hyponatraemia due to the syndrome of inappropriate secretion of antidiuretic hormone (SIADH) (plasma sodium 124 mEq/l, urinary sodium 182 mEq/l, plasma osmolality 262 mosmol/l, urine osmolality 775 mosmol/l, vasopressin 1.86 pg/ml; and normal renal, thyroid, and adrenal function). Liver function was normal, and blood hepatitis C virus RNA was negative. Immunoglobulins and complements were normal. Cryoglobulin, M-protein, antinuclear antibody, and anti-SS-A/-B antibodies were negative. We examined various antiviral antibodies (coxsackie viruses, herpes simplex virus, varicella zoster virus, cytomegalovirus, Epstein-Barr virus, measles, rubella, mumps, adenovirus, and influenza A and B) in the serum or CSF, measles, rubella, mumps, adenovirus, and influenza A and B) in the serum or CSF, but they showed no remarkable change. Several tumour markers in the serum also showed no particular change. Serum IgG class anti-GQ1b antibody was present with low titre as demonstrated by enzyme linked immunosorbent assay (ELISA). Immunohistochemistry using frozen sections of rat cerebral cortex, cerebellum, spinal cord, and dorsal root ganglion showed no antineuronal antibody in the serum from the patient, although the serum from a patient with anti-Hu antibody positive paraneoplastic syndrome showed positive reactions with these neurons (data not shown). ELISA for anti-Hu antibody was negative in the serum and CSF. His CSF showed an increased protein concentration (159 mg/dl) without pleocytosis but no oligoclonal bands.

Brain and spinal MRI were normal. Whole body CT examination; colon fibroscopy and a ¹⁸Ga-citrate scintigram showed no malignancy.

On neurophysiological studies, an EEG showed delta bursts in all leads. Motor conduction velocity and amplitude of compound muscle potentials in the right median, ulnar, and posterior tibial nerves were within the normal range. By contrast, sensory nerve action potentials (SNAPs) could not be elicited in right median and sural nerves. In the right ulnar nerve, amplitude of SNAPs was markedly decreased (3 µV) with preservation of sensory conduction velocity (53.3 m/s). A needle EMG gave normal results. Sympathetic skin response could not be elicited in the upper and lower limbs. The coefficient of variation of R-R intervals on ECG was decreased (1.17% at rest; mean value and lower limit in the 50s age group 2.80, 1.41). The sural nerve biopsy disclosed marked axonal degeneration with a significant decrease of both myelinated (1359/mm²) and unmyelinated fibres (13 791/mm²) (figure).

There was no inflammatory cell infiltration or vasculitis. The patient was treated with plasmapheresis (3000 ml/3) beginning on 6 October. Soon after the plasmapheresis, joint sensation in his fingers was slightly improved and anisocoria disappeared. Plasma sodium concentration, the patient’s level of consciousness, and the EEG were subsequently normalised. After the plasmapheresis, he was treated with steroids (methylprednisolone (1000 mg intravenously), for the first 3 days, and then prednisone (60 mg orally), followed by a gradual taper). This did not further improve his symptoms; severe sensory impairment, orthostatic hypotension, and constipation persisted 3 months after the onset of the disorder.

Our patient presented with acute onset of sensory impairment, autonomic dysfunctions, selective impairment of sensory and autonomic nerves in electrophysiological studies, and a raised CSF protein concentration. These clinical features are compatible with a diagnosis of AASN. In addition, our patient showed SIADH and consciousness disturbance suggestive of involvement of the CNS.¹

In AASN, episodes of infection before the onset are often seen, suggesting that preceding infection may induce the immediate process leading to AASN. Pavesi et al described a patient with Coxsackie B virus infection complicated by an acute autonomic and sensory neuropathy.¹ In their patient, diffuse mucosal and cutaneous erythema preceded neurological complications. Our patient also presented a cutaneous lesion followed by an autonomic and sensory neuropathy. However, serum and CSF studies for antiviral antibodies showed no evidence for any viral infection.

Peripheral neuropathy is a rare neurological side effect of interferon. There have been reports of multiple mononeuropathy, acute motor or sensorimotor axonal polyneuropathy, and cranial nerve palsies. Although the pathomechanism underlying peripheral neuropathy associated with interferon is unknown, immunomodulatory effects of interferon may cause disorders of the peripheral nervous system.¹

In our patient, AASN developed after the interferon therapy with an increased protein concentration in the CSF, and plasmapheresis seemed to result in slight improvement and prevention of the disease progression. This is the first report suggesting association of interferon and AASN. We suggest that interferon may induce an immune mediated
damage to the autonomic and sensory ganglion neurons leading to clinical manifesta-
tion of AASN.

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Neuropathic pain with vesical and rectal
hyperreflexia and cocontraction after
pelvic surgery

Pelvic and pudendal nerve injury can occur
during extirpative visceral surgery such as
radical hysterectomy.1,2 Many of these
patients develop severe chronic pelvic pain
and bladder symptoms, and are often referred
to neurologists with suspicion of lumbosacral plexus lesions or disc disease. There are few or no signs on examination, and patients are often considered to be “hys-
terical”, despite having severe symptoms. Here, we describe two patients in whom severe pelvic pain and bladder dysfunction developed after hysterectomy, and who dem-
onstrated detrusor and rectal hyperreflexia with cocontractions, features usually associ-
ated with lesions of the CNS. Whereas spinal cord sensitisation is well recognised after
somatic nerve injury, our studies provide the first clear evidence for its development after
visceral nerve injury in humans, and a method for its detection using ambulatory
urorectodynamics.

Patient 1, a 42 year old woman, was diag-
nosed as having carcinoma of the cervix 5
years previously and underwent Wertheim's
hysterectomy, followed by chemothera-
py and pelvic irradiation. She developed severe persistent vaginal pain and hypersensitivity, which prevented her from having sexual intercourse, and subsequently bladder dys-
fuction, which required intermittent self-
atriatherisation. She received several analge-
sic drugs without benefit. Neurological and
pelvic examination and spinal imaging, were
normal. An ambulatory urorectodynamics study (after prior written informed consent) showed vesical instability associated with unstable urethral function; simultaneous abnormal rectal contractions, and falls in
anal pressure.

These patients had severe symptoms but
no clinical signs, and abnormalities were
detected only after pudendal nerve conduc-
tion and urorectodynamics studies, which
disclosed visceral hyperreflexia in both cases. Patient 1 probably had injury to the pelvic nerves, which is well recognised after exten-
sive hysterectomy.1 Patient 2 had pudendal nerve damage, supported by the nerve conduction study. Our patients did not have neurological signs suggestive of CNS lesions, but demonstrated features usually associated
with such lesions, namely detrusor and rectal
hyperreflexia. Visceral hyperreflexia can oc-
cur after spinal cord lesions and in the
absence of obvious neurogenic lesions but its
occurrence after peripheral nerve damage is
not well recognised.1,3

The likely explanation for visceral
hyperreflexia in our patients is increased barrage originating from injured sensory
nerves, leading to spinal cord sensitisation; this mechanism is well established after
somatic peripheral nerve injury, but barely
considered after pelvic surgery.4 Persistent visceral noxious input to the spinal cord
could lead to reflex activation of the intermediolateral cell column,5 the increased
output of which may in turn increase bladder
and rectal contractions. Other relevant evi-
dence of spinal cord disinhibition in our
patients is the loss of the normal inhibition

Figure 1 Eight minute trace from first ambulatory study on patient 1, showing uninhibited vesical contraction, urethral instability, and abnormal rectal
contraction associated with a fall in anal pressure. Note simultaneous vesical and rectal contractions (cocontractions).
of urinary bladder contraction induced by rectal and vaginal stimulation and the development of bladder and rectum cocontractions, which have not been reported previously.

Our cases show how pelvic surgery could be complicated by persistent neuropathic pain and bladder and bowel hypersensitivity, and further studies of spinal cord excitability are needed to clarify underlying mechanisms. Early recognition and initiation of analgesic treatment for neuropathic pain is essential to prevent the condition becoming intractable.

Peripheral nerve ischaemia after internal iliac artery ligation

Ligation of the internal iliac (hypogastric) arteries has been used to control severe obstetric and pelvic bleeding. It is generally well tolerated in the young obstetric or gynaecological patient, presumably because of an extensive collateral blood supply.1 Acute lumbosacral plexopathies have been described, however, in older patients with vascular disease when the internal iliac arteries are interrupted.2 3 We report on a teenage patient with similar peripheral nerve ischaemia after bilateral internal iliac artery ligation for postpartum haemorrhage.

An 18 year old woman presented at 40 weeks gestation with mildly raised blood pressures, trace proteinuria, oliguria, and generalised oedema. She was diagnosed with pre-eclampsia and admitted for induction. When induction was unsuccessful, she underwent a caesarean section, which was complicated by uterine atony and a postpartum haemorrhage with an estimated blood loss of 2500 ml. After bilateral uterine artery ligation failed to control the bleeding, bilateral internal iliac artery ligation was performed with resultant haemostasis.

On the first postoperative day, she complained of left buttock pain and difficulty moving her leg. The vastus lateralis, tibialis anterior, gastrocnemius, and vastus medialis in one patient and of the tibialis anterior and gastrocnemius in another. Low amplitude polyphasic motor units in the vastus lateralis suggested early proximal muscle necrosis. Magnetic resonance imaging of the thoraco-lumbar spinal cord was unremarkable. An initial magnetic resonance angiogram (MRA) of the pelvis showed segmental occlusions of both internal iliac arteries with distal reconstitution greater on the right than on the left. The left superior gluteal artery was not visualised. Revascularisation was considered but deferred due to the concomitant active pelvic infection. Peripheral pulses remained strong, and Doppler ultrasounds showed no evidence of distal thrombus.

Nerve conduction studies 1 week after ligation were extremely limited and difficult to interpret due to generalised oedema. Sural and peroneal sensory responses were absent bilaterally. Right peroneal and left tibial motor responses were normal. A small left peroneal motor response was present in the anterior tibialis muscle. Electromyography was not performed at that time.

The fevers and endometritis gradually cleared, and over the next month left leg strength improved slowly, but incompletely, with greater proximal (4–5 in hip flexion and knee extension, 3 in knee extension) and 3 to 4/5 on ankle plantarflexion, ankle dorsiflexion, and toe extension. Sensation was diminished to all modalities in the entire left leg below the hip. The left patellar and ankle stretch reflexes were absent.

Magnetic resonance imaging of the region disclosed additional soft tissue necrosis subcutaneously along the left posterior lateral buttock and inflammation in the surrounding subcutaneous tissues and underlying gluteal musculature with extension into the left sacroiliac joint. There was no evidence of rectal, uterine, or bladder ischaemia.

A follow up MRA of the pelvis 6 weeks after ligation demonstrated persistent segmental occlusion of both internal iliac arteries and left superior gluteal artery on the left compared with the right. Again, the superior gluteal artery was not visualised on the left but appeared to fill on the right.

Electromyography of selected muscles of the left leg at 12 months (after ligation) showed 2+ to 4+ fibrillations and positive sharp waves in the vastus lateralis, tibialis anterior, and lateral gastrocnemius muscles, consistent with axon loss and denervation. There were no voluntary units in the tibialis anterior and low firing rates in the gastrocnemius. Low amplitude polyphasic motor units in vastus lateralis suggested early proximal recovery. Nerve conduction studies showed diminished left sural sensory amplitudes and slowed velocities (2.8 mV, 36.0 m/s). The left peroneal motor response was attenuated, and the left posterior tibial motor velocities were slowed (32.0 m/s). The right sural sensory (13.2 µV, 42.0 m/s) and peroneal motor (2.3 mV, 46.0 m/s) responses were normal.

In general, the internal iliac artery divides into an anterior and a posterior division. The anterior division is formed by the inferior gluteal artery and its branches, which supply the pelvic viscera, the lower back, and the back of the thigh. The posterior division is formed by the superior gluteal artery and its branches, which supply the gluteal musculature, the femoral nerve, and the sciatic nerve roots.

Ligation of the internal iliac arteries has been accepted as a safe and effective means of controlling serious haemorrhaging from the uterus or lower pelvis after delivery or after gynaecological surgery.4 5 The lack of ischaemic complications from ligation of the internal iliac artery is thought to be due to the multiple sources of collateral blood flow present in the pelvis. There are, however, reports of buttock ischaemia or lumbarosacral plexopathies as a complication of interruption of the internal iliac arteries during aortic bypass procedures or aortoiliac aneurysm resection.6 7 In a study of 11 patients (mean age 67, range 37 to 87) with aortoiliac occlusive disease or aortoiliac aneurysmal disease, seven developed ischaemic injury to the lumbarosacral plexus after bilateral internal iliac artery ligation.8 In four of those patients, buttock necrosis with extension to the bony pelvis was also seen. In another report, four women (mean age 57, range 33 to 47) with insulin dependent diabetes and end stage renal disease developed ipsilateral lumbarosacral plexopathy when the internal iliac artery was ligated during kidney transplantation.9 Electromyography showed denervation of the tibialis anterior, gastrocnemius, and vastus medialis in one patient and of the tibialis anterior and gastrocnemius in another. Ischaemia of the sciatic and femoral nerves and buttocks also occurred after internal iliac artery embolisation in patients with terminal pelvic malignancies who received radiotherapy.9

Our 18 year old patient developed a combination of leg weakness, leg numbness, and buttock necrosis after internal iliac artery ligation, as described in older vasculopathic patients. In the patients described in the literature, as in our patient, the clinical and electromyographic findings do not distinguish between combined form and sciatic nerve lesions, a lumbarosacral plexopathy, or a combination of the two. Our patient's presentation, however, can be most succinctly explained by an infarction in the territory of the left superior gluteal artery and its branches, resulting in ischaemia to the gluteal musculature, the femoral nerve proper, and the sciatic nerve roots. This localisation is supported by serial MR angiograms of the pelvis in which the left superior gluteal artery and its branches were not visualised.

It has been shown that, in experimental ligation of the internal iliac artery in rats, moderate sciatica is associated with denervation.
Diffusion weighted magnetic resonance imaging in Neuro-Behçet's disease

Neurological involvement is one of the most devastating manifestations of Behçet's disease. However, the pathogenic mechanism for CNS lesions in patients with neuro-Behçet's disease is unclear. Although vasculitis is usually considered to be the central pathological feature in Behçet's disease, a vasculitic process was not usually demonstrated in the CNS.

Diffusion weighted imaging can detect changes in water diffusion associated with cellular dysfunction. It has been well documented that acute infarction related to cytotoxic oedema is characterised by a marked decrease in diffusion, and also that increased interstitial water related to oedematous oedema shows increased diffusion. Conventional MRI cannot distinguish between these different types of oedema. We report on a patient with neuro-Behçet's disease with a significantly reversible T2 signal and diffusion abnormalities in CNS lesions.

A 54 year old Asian man was admitted with dysarthria and left hemiparesis, which evolved over a period of 2 days and was associated with gradual mental deterioration. The patient had a history of frequent orogenital ulcers and acneiform nodules on his face. Physical examination showed active genital ulceration. Neurological examination disclosed drowsy consciousness and disorientation. Moderate degrees of hemiparesis and hemihypaesthesia involving the face, arm, and leg were found on the left side. Deep tendon reflexes were increased and Babinski's sign was extensor on the left side. Erythrocyte sedimentation rate (54 mm/h) and C-reactive protein concentration (3.4 mg/100 ml) were increased. Examination of CSF showed mild pleocytosis (18 white blood cells/mm³) with normal concentrations of protein and glucose. Fundus examination showed retinal vein occlusion and retinal haemorrhage on the right side. The diagnosis of Behçet's disease was made based on the recurrent orogenital ulcerations, skin lesions, and eye involvement.

The patient was examined on a 1.5T MR unit (Sigma Horizon, Echospeed; General Electric Medical Systems) with echoplanar imaging (EPI) capability. Fast spin echo, T2 weighted images (T2 weighted images; TR/TE 4200/112 ms; field of view 21×21 cm; matrix 256×192; and slice thickness 5 mm) were obtained. Diffusion weighted imaging was obtained in the transverse plane using a single shot EPI (TR/TE 6500/125 ms; field of view 24×24 cm; matrix 128×128; slice thickness 5 mm; and two b values 0 and 1000 s/mm²). The diffusion gradients were applied along the three axes (x, y, z) simultaneously. The apparent diffusion coefficient (ADC) was calculated based on the negative slope of the linear
regression line best fitting the points for $b$ versus $a$ (SI); where SI is the signal intensity from a region of interest within the images acquired at each $b$ value. Performing this calculation on a pixel by pixel basis created the ADC maps.

Brain MRI performed 3 days after symptom onset showed extensive T2 hyperintensities involving the corona radiata, internal capsule, basal ganglion, thalamus, and midbrain on the right side. Brain diffusion weighted imaging showed slight hyperintensities which were limited to the corona radiata, the medial portion of the basal ganglion, and the thalamus. Four sampled ADCs in the corresponding regions of T2 hyperintensity demonstrated increased diffusion (ranging from 1.17 to 1.26 ×10⁻⁵ cm²/s), compared with a matching location in the uninvolved contralateral hemisphere (ranging from 0.77 to 0.80×10⁻⁵ cm²/s, figure A and B). Magnetic resonance angiography showed no abnormalities. The patient improved rapidly after treatment with a high dose of corticosteroid. Within 2 weeks all previously noted neurological abnormalities had resolved except for a slight left hemiparesis. An MRI repeated at this time showed a partial decrease in the extent of the T2 hyperintensity. One year later he was readmitted with a slowly progressive bulbar weakness, frontal lobe dysfunction, urinary incontinence, and depressive mood changes. Follow up MRI performed at this time, showed that the previous T2 abnormalities had improved, but the atrophy of the brain stem and basal ganglia became evident with periventricular high signal intensities. Four ADCs sampled in locations corresponding to those of the initially increased ADCs decreased to values which ranged from 0.98 to 1.07 ×10⁻⁵ cm²/s (figure C and D).

In our patient the ADC maps and ADC values showed high proton mobility, which suggests vasogenic oedema in acute lesions of neuro-Behçet's disease. Vasogenic oedema develops when the blood-brain barrier is disrupted and is not primarily associated with cellular damage. Discrimination between cytotoxic and vasogenic oedema has important clinical implications because vasogenic oedema can be reversed by proper management.

According to the MRI findings for neuro-Behçet's disease, the most prevalent abnormalities are located in the brain stem or the basal ganglia extending to the diencephalic structures during an acute attack, and brainstem atrophy in chronic cases. The reversibility of CT or MRI abnormalities of acute lesions in neuro-Behçet's disease has also been documented and correlated with clinical improvement. The serial MRI findings in our patient were consistent with those described in previous reports. The precise pathomechanism of CNS lesions in Behçet's disease has not been established. Studies of pathology showed that lymphocytic or neutrophilic meningoencephalitis with perivascular inflammatory cell cutting around venules and capillaries were predominant in the brain stem and basal ganglia in neuro-Behçet's disease. However, most studies showed histopathological changes at a chronic stage of the disease and histopathological findings may show various types of lesions according to the age of lesion at the time of examination. A recent pathological report in a fulminant form of neuro-Behçet's disease found no evidence of vasculitis but an acute destructive inflammatory process. It has been postulated that at an early stage of the disease, the reversibility of lesions may reflect a reversible breakdown in the blood-brain barrier rather than gliosis or infarction. The pattern of diffusion changes in the acute lesions in our patient strongly supports the idea that there is increased permeability in the blood-brain barrier as a result of the primary inflammatory process.

We thank Byung Kee Yoo for his assistance with diffusion weighted MR data acquisition.

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Data of patients before and after treatment

<table>
<thead>
<tr>
<th></th>
<th>IFN</th>
<th>AZA</th>
<th>NT</th>
</tr>
</thead>
<tbody>
<tr>
<td>No of patients</td>
<td>11</td>
<td>10</td>
<td>11*</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>3/8</td>
<td>2/8</td>
<td>3/8</td>
</tr>
<tr>
<td>Age (entry)</td>
<td>33 (6.2)</td>
<td>31.2 (4.9)†</td>
<td>31.2 (4.9)†</td>
</tr>
<tr>
<td>Disease duration</td>
<td>8.3 (5)</td>
<td>6.95 (6.7)</td>
<td>8.4 (6.8)‡</td>
</tr>
<tr>
<td>EDSS at entry</td>
<td>2.32 (0.9)</td>
<td>2.35 (0.9)</td>
<td>1.83 (1.15)</td>
</tr>
<tr>
<td>At 12 months</td>
<td>2.2 (1.0)‡</td>
<td>2.1 (0.9)‡</td>
<td>1.9 (1.3)‡</td>
</tr>
<tr>
<td>No of worsened patients at 12 months</td>
<td>1/11</td>
<td>0/10</td>
<td>2/10</td>
</tr>
<tr>
<td>RF 2 year pretreatment</td>
<td>2.2 (0.8)‡</td>
<td>2 (1)</td>
<td>1.4 (0.3)‡</td>
</tr>
<tr>
<td>At 12 months</td>
<td>0.8 (0.7)‡</td>
<td>0.9 (0.4)‡</td>
<td>1.0 (0.9)‡</td>
</tr>
<tr>
<td>No of relapse free patients at 12 months</td>
<td>4/11</td>
<td>7/10</td>
<td>4/10</td>
</tr>
<tr>
<td>PCH at entry</td>
<td>68.02 (9.1)</td>
<td>61.7 (10.8)</td>
<td>61.7 (11.7)</td>
</tr>
<tr>
<td>Change at 12 months</td>
<td>+7.9 (9.8)</td>
<td>+6.25 (14.5)</td>
<td>+5.87 (16.9)</td>
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<tr>
<td>MHC at entry</td>
<td>74.7 (15.7)</td>
<td>61.25 (14.5)</td>
<td>58.7 (16.9)</td>
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<tr>
<td>Change at 12 months</td>
<td>+6.04 (13.9)</td>
<td>+21.25 (11.9)</td>
<td>+6.37 (21.8)</td>
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<tr>
<td>REL at entry</td>
<td>83.34 (32.4)</td>
<td>37.5 (33.05)</td>
<td>55.55 (40.8)</td>
</tr>
<tr>
<td>Change at 12 months</td>
<td>+10 (35.3)</td>
<td>+49.35 (36.5)</td>
<td>+16.0 (53.4)</td>
</tr>
</tbody>
</table>

Summary:

1. Significant differences between groups:
   - Age at entry: NT vs AZA p=0.01.
   - RF at entry: NT vs IFN p=0.006.
   - MHC change: IFN vs AZA p=0.006.
   - REL change: IFN vs AZA p=0.001.

2. The two composite scores mental health and physical health were also evaluated. A test for unpaired samples was used to compare the scores between groups, with adjustment for multiple comparisons. The Kruskal–Wallis test and the two sample Wilcoxon rank sum test were used to compare the change in scores between groups. The main clinical variables were compared using $t$ for unpaired and paired data.

Thirty two patients were included in the study (11 IFN-1b, 10 AZA, 11 NT). The clinical characteristics at entry were similar in the two actively treated groups, whereas in the NT group age was significantly higher than in the AZA group (but not the IFN group) and pretreatment relapse frequency (RF) was lower than in the IFN group (but not the AZA group). After 1 year, RF significantly decreased in both the active treated groups compared to the NT group.

For a full reference list, please see the published article.
IFN and AZA treated groups without differences between the two treatments, whereas it was unchanged in the NT group. The EDSS remained stable in the three groups (table). Five of 11 patients treated with IFN had flu-like symptoms on one or more occasions, whereas no side effects occurred in the other two groups.

No significant differences in the HD scores and quality of life profile were found between the three groups at entry. At 6 (data not shown) and 12 months the mental health composite score significantly increased in patients treated with AZA compared with the patients treated with IFN, mainly due to the increase in role limitation for emotional reasons item; no significant differences between the NT group and actively treated groups were seen. No significant changes in HD scores in the three groups were found at 12 months. These results suggest that both AZA and IFN-J-1b are effective in reducing relapse frequency in patients with RRMS. The treatment effect on quality of life has been rarely investigated, with conflicting results: no significant change after 1 year of IFN.

In our study, the impact on quality of life was better in patients treated with AZA than in those treated with IFN, mainly due to the improvement in mental score. A direct effect of the drugs on the CNS seems unlikely: no symptoms of neurotoxicity were found in either treatment group and no patients developed depression according to the HD scale. Most likely the improvement of quality of life in patients treated with AZA might be related to different tolerability or to differences in treatment schedules, resulting in a more pronounced and persistent perception of the disease in patients treated with IFN. Due to the few patients, the results of this study need to be verified by a larger randomised comparaative trial.

We are indebted to Dr Alessandra Solari, Laboratory of Epidemiology, C Besta National Neurological Institute, Milan, Italy, for performing the statistical analysis of the data.

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Unilateral caudate head lesion simulating brain tumour in X-linked adult onset adrenoleukodystrophy

The appearance of X-linked adrenomyeloneuropathy (AMN)/adrenoleukodystrophy (ALD) on MRI is usually specific, with bilateral symmetric areas of white matter abnormality surrounding the posterior horns of the lateral ventricles with various degrees of atrophy of the spinal cord.7 Our patient with AMN, however, showed a lesion in the right caudate head simulating a brain tumour, which has not been a feature in this disease.

At the age of 25 the patient started to have progressive spastic paraparesis and mild ataxia with genitourinary dysfunction (urge urinary incontinence and erectile dysfunction).7 On admission to our hospital at the age of 34, T2 weighted MR images showed small lesions in the bilateral internal capsule although no abnormality was seen in the spinal cord. Nerve conduction studies and the sural nerve biopsy showed evidence of peripheral nerve involvement. A low serum cortisol response to intravenous adrenocorticotrophic hormone and increased concentration of plasma very long chain fatty acids were consistent with a diagnosis of AMN. Three years later he showed marked emotional lability. T2 weighted MRI showed a high signal mass lesion in the right caudate head and the ipsilateral anterior internal capsule which simulated an intracranial tumour, without marked demyelination in the surrounding deep white matter (fig 1). A year later he became wheelchair bound, apathetic, and demented. Brain MRI showed right sided dominant white matter abnormalities and atrophy of the spinal cord. Three years later he died of respiratory infection and necropsy was performed. Pathological examination showed frontotemporal cortical atrophy with diffuse white matter demyelination including bilateral internal capsules, where astrocytes proliferated and lipid laden macrophages infiltrated around the small vessels. Neurons were moderately shrunken and the neuropil showed tissue rarefaction. Demyelination was also seen in the cerebellar white matter. The caudate head showed bilateral but right side dominant atrophy, where neuronal loss and tissue rarefaction with fibrillary gliosis (spongy state) were seen (fig 2).

Previous reports of X-ALD/AMN showed occasional unilateral basal ganglia involvement. Affifi et al reported on a 4.8 year old boy whose MRI showed a right anterior white matter lesion extending into the ipsilateral putamen and the thalamus.3 Close et al described an 8 year old boy who had a left occiptotemporal white matter lesion extending into the ipsilateral thalamus on MRI.4 However, the imaging pattern in our patient is unique because of the high signal mass lesion in the right caudate head and the ipsilateral anterior internal capsule without marked demyelination in the surrounding white matter, falsely suggestive of a brain tumour. There are also other demyelinating disorders simulating brain tumour which include multiple sclerosis.3 The findings indicate that plasma very long chain fatty acid

Figure 1 Brain MRI of the patient at the age of 37. T2 weighted MR images showed a high signal mass lesion in the right caudate head and the ipsilateral anterior internal capsule which simulated an intracranial tumour, without marked demyelination in the surrounding deep white matter.

Figure 2 Microscopic section of the right caudate head (haematoxylin-eosin staining, originally×50). This shows neuronal loss and tissue rarefaction with fibrillary gliosis, presenting as spongy with little inflammation.
concentrations should be measured in patients with unexplained basal ganglia abnormalities on MRI.

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Clinical data of patients with multiple sclerosis treated with glatiramer acetate

**Table:**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Annual relapse rate at start</th>
<th>Annual relapse rate in study</th>
<th>EDSS at start of study</th>
<th>EDSS at end of study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymph node swelling</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.8 (1–3.5)</td>
<td></td>
<td>0.33 (0–1)</td>
<td>2.5 (0–3.5)</td>
<td>2.5 (0–3.5)</td>
</tr>
<tr>
<td>No lymph node swelling</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.5 (1–3.5)</td>
<td></td>
<td>0.54 (1–1.8)</td>
<td>2.5 (1–3.5)</td>
<td>3.0 (0–6.5)</td>
</tr>
</tbody>
</table>

Values are mean (relapse rate) or median (EDSS) (range).
The remedial approach, Further to the excellent review of neurovisual rehabilitation in Balint’s syndrome by Kerkhoff, we think that it is prudent to communicate our experiences in the management of a patient with Balint’s syndrome after traumatic brain injury. This was seen in a 41 year old right-handed manual worker whose initial cranial CT showed right extradural haematoma. Subsequent scans demonstrated left posterior occipital infarct. Brain MRI 3 months after the injury showed high signal in the right occipito-parietal and left occipitotemporal regions. His physical recovery was satisfactory in that he was fully mobile unaided. However, he presented with simultanagnosia, optic ataxia, and psychic paralysis of gaze. This had an adverse impact on his functional independence; he had difficulty finding objects in his environment, and was unable to use furniture and walls—and other activities of daily living including dressing and toileting. He failed most subtests in the Rivermead perceptual assessment battery (RPAB). We agree with the author that effective treatment strategies are poorly developed and evaluated. We have identified three approaches for the rehabilitation of the perceptual deficits including those seen in Balint’s syndrome.

- The adaptive (functional) approach, which involves functional tasks utilising the person’s strengths and abilities, helping them to compensate for problems or altering the environment to lessen their disabilities.

- The remedial approach, which involves restoring some of the damaged CNS by training in the perceptual skills, which may be generalised across all activities of daily living. This could be achieved by tabletop activities or sensorimotor exercises.

- The multicontext approach, which is based on the fact that learning is not automatically transferred from one situation to another. This involves practising of a targeted strategy in a multiple environment with varied tasks and movement, and it incorporates self-awareness tasks.

In this patient, we used the adaptive approach, practise functional tasks repeatedly using increasing complexity of the tasks as the sessions continued. This approach assumes that treatment has little effect on impairment and that generalisation to other tasks is unlikely. It also assumes that the brain has limited ability to improve and restore itself after injury. The remaining abilities are used to offset the deficits. This patient was able to develop his own compensatory strategies, learned to use his hands to acquire tactile feedback, and managed to direct his gaze to visually locate objects when required. His performance on the RPAB was improved and he was successfully discharged home with little support.

As Balint’s syndrome is likely to be seen in clinical conditions such as Alzheimer’s disease, multiple sclerosis, intracranial tumours, brain injury, and CNS complications of HIV infection, we thought it important to outline the possible options for the management of this condition. Further work is required on a larger series of patients.

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Kerkhoff replies
Al-Khawaja and Haboubi have reported successful neurovisual rehabilitation in a patient with Balint’s syndrome due to a right occipito-parietal and left occipitotemporal lesion, using adaptive practising of functional tasks with increasing complexity. This case shows, together with some of the other published cases, that individually tailored rehabilitation strategies can be adapted successfully for patients with Balint’s syndrome. Due to the various aetiologies and subsequent lesion localisations, it is likely that most patients with Balint’s syndrome will have some outstanding deficits, but also some spared abilities, which can be used for compensatory purposes (for example, intact tactile feedback).

In two patients with Balint’s syndrome treated for several months in our department, significant improvements could be achieved by systematic treatment so that both patients could live independently at home with only minimal assistance. One patient, who had severe traumatic, urogenital, and hypoxic brain damage at the age of 27 years initially was nearly blind. Two years later, when treatment started in our unit, he couldn’t perceive more than two visual stimuli simultaneously (simultanagnosia), was almost unable to read, showed optic ataxia, and had severely impaired spatial-perceptual functions in the visual and tactile modality. However, his memory, intelligence, and executive functions were largely preserved, so that he relearned reading partially, learnt to dress himself partially, and was finally able to travel by train. He managed to live alone in his flat, with only minor assistance from others.

The second patient, a 60 year old physician, had bilateral vascular parieto-occipital lesions. She was initially (falsely) considered as blind, although she could well see and describe faces and correctly identify the colour of one’s eyes. She presented with severely disturbed depth and horizontal distance perception, simultanagnosia, and optic ataxia as well as a peculiar deficit in identifying spatial directions and locating sound sources. For instance, it proved difficult for her to identify the direction in which someone pointed when describing a particular route, or to decide in which direction a train would move when looking at the railway track. However, as in the first patient, she had some spared abilities—that is, excellent introspection and awareness of her disorder, preserved cognitive abilities, and she was highly motivated to learn route finding in her town district. After intensive training for reading and route finding she could be discharged, living independently at home. She continues to use public transport to go shopping, visit friends, see her neurologist, the pharmacist, or going to a concert hall.

I think that systematic treatment in both cases helped to improve basic visual abilities and activities of daily living so that both patients could live independently at home, which was hardly expected when seeing them at the onset of treatment. To conclude, I am convinced that many patients with Balint’s syndrome can learn to compensate for at least some of their visual deficits by systematic and individualised treatment. The search for spared functions will undoubtly disclose multiple ways for compensation and will increase our understanding of some unresolved aspects of this fascinating syndrome—for example, the tactile or auditory-spatial abilities of patients with Balint’s syndrome.

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The authors state that their second publication (Kerkhoff G. Neurovisual rehabilitation: recent developments and future directions. J Neurol Neurosurg Psychiatry 2000;68:691–706) has been cited by Al-Khawaja and Haboubi in their paper. However, the citation is not accurate as the authors did not cite the reference. The correct citation should be Kerkhoff G. Neurovisual rehabilitation: recent developments and future directions. J Neurol Neurosurg Psychiatry 2000;68:691–706.
scleral search coil technique. I suspect that it would have shown a torsional component and that this patient also had jerk-waveform see-saw nystagmus.

Jerk-waveform see-saw nystagmus occurs with unilateral mesodiencephalic lesions, presumed due to selective unilateral inactivation of the torsional eye velocity integrator in the interstitial nucleus of Cajal; during the fast [jerk] phases the upper poles of both eyes rotate toward the side of the lesion. With lateral medullary injury the fast phases of the torsional component jerk away from the side of the lesion. In both situations the torsional component is always conjugate. With mesodiencephalic lesions the vertical component is always disjunctive, but with medullary lesions it may be either conjugate (usually upward) or disjunctive.

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The authors reply:
We thank Lavin for his interesting comments. We stated in our article that the possibility of a fine see-saw nystagmus could not be excluded. We did re-evaluate our patients with a torsional coil and did not record a torsional component. However, because of the fast improvement in both patients, all the eye movement abnormalities on re-evaluation were minimal. Clinically, even in the stage of maximal abnormalities, in one patient we did not detect any torsional component, which suggests that if there was an element of see-saw nystagmus, it was subclinical.

We did not state that the type of nystagmus associated with the Arnold-Chiari malformation was unique, precisely because we could not rule out with total certainty a see-saw nystagmus, which has been reported in one patient with the malformation. We did, however, point out that this association is unusual.

Because of the lack of strong evidence of a torsional component to the dissociated vertical nystagmus, we preferred the term, kindly suggested by a reviewer, “nystagmus of skew”. This would represent a more inclusive, descriptive term, of which both the pendular and the jerk see-saw nystagmus forms and the dissociated vertical nystagmus without demonstrable torsional component would represent subvariants.

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Fig 1 Scintigraphy of the head of patient 1 showing technetium 99m uptake one day before (left) and 7 days after (right) retrograde transducatal BoNT/A injection into the salivary glands, showing significant reduction of tracer uptake after the BoNT/A injection (quantification: parotid gland left –59%, right –48%; sublingual gland left –10%; right –56%).

Botulinum toxin for the treatment of sialorrhoea in ALS: serious side effects of a transducatal approach

We have read with interest the article by Giess et al. which showed that botulinum toxin A (BoNT/A) might be a new treatment option for sialorrhoea in patients with bulbar palsy. We have recently conducted a similar study which was interrupted due to serious side effects.

In September 1998 we injected 25 MU Botulin into the parotid glands of a 59 year old women who had ALS with pronounced bulbar palsy. We noticed a reduction of the sialorrhoea but facial weakness on the left side worsened significantly.

After this experience we developed a protocol for the treatment of sialorrhoea in patients with ALS with bulbar palsy by retrograde injection of BoNT/A through the salivary duct into the salivary glands. We chose the retrograde way of administration of BoNT/A for this pilot study because we thought that this technique would avoid facial weakness.

After informed consent the patients received 12.5 mouse units (MU) Botulinum toxin A (BoNT/A) retrogradly into each parotid and sublingual gland from a small catheter inserted into the salivary duct. Neurological examination and quantification of salivary production were performed before the BoNT/A injection and on days 1, 3, 7, 14, and 28, as well as after 2 and 3 months. Technetium 99m scintigraphy was performed before the injection (76% and 58%; from 5420 mg to 1301 mg, and 4365 to 1829 mg) which lasted for 4 to 8 weeks. Technecium 99m scintigraphy showed a significant reduction of radiotracer uptake into the injected salivary glands in both patients (figure). Both patients estimated the injection procedure as painful. Patient 1 developed a severe swelling of the right sublingual salivary gland and base of the tongue 3 days after the injection which was treated with antibiotics and corticosteroids. Patient 2, who was able to swallow with difficulty before the injection, mentioned impairment of swallowing between days 4 and 21. Both patients had a “moderate” improvement of sialorrhoea but did not want the injections to be repeated. After these experiences we decided to stop the pilot study.

The injection of BoNT/A through the salivary duct reduces the activity of the salivary glands significantly for several weeks but has serious side effects. Local and systemic effects of BoNT/A are probably pronounced in ALS. Subclinical EMG abnormalities distant to the injection sites have been described in therapeutic doses, but also systemic weakness has been found. As there are some reports that BoNT/A injections, even in low doses, may exaggerate pre-existing neuromuscular diseases, careful monitoring of neurological symptoms, which is difficult in a progressive disease, is needed to exclude side effects of BoNT/A. The drug is effective in reducing drooling but we need more data about the safety of BoNT/A before it can be used safely for the treatment of sialorrhoea in ALS. The transducatal approach in particular seems to have unacceptable side effects.

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Treatment of early onset Parkinson’s disease with botulinum toxin A

The recent editorial supporting initial treatment of early onset Parkinson’s disease with a dopamine agonist hinged in part on the demonstration in 268 patients that treatment of early onset Parkinson’s disease with ropinirole alone or with supplementary levodopa/dopamine decarboxylase inhibitor (benserazide) (LD/DDI) resulted in substantially less dyskinesia than with LD/DDI alone, with only slightly less motor benefit. Five per cent of patients on ropinirole alone developed dyskinesia after 5 years, compared with 25% with ropinirole plus LD/DDI, and 45% of those on LD/DDI alone. The trial design allowed LD/DDI supplementation if response was inadequate and additional trial drug could not be tolerated. Up to 24 mg ropinirole and 1200 mg LD/DDI daily were allowed. Sixty six per cent of patients completing the ropinirole arm required supplementation, the average mean daily dose of ropinirole at 5 years being 16.5 mg, compared with 753 mg of LD/DDI when the second-on was used alone.

It is unfortunate that the study required a three times daily dosage regime. It seems possible that this accounts for the surprising 33% of patients on LD/DDI alone who withdrew as a result of early complications and events, and for the occurrence of nausea in 49.4% of patients on LD/DDI alone. Whether smaller, more frequent, dosage would have allowed better tolerance of and motor response to ropinirole, it is uncertain. That frequent dyskinesia was seen at 5 years on three times daily dosage of LD/DDI. A substantial proportion of patients on LD/DDI (43.8%) were also on selegiline, amplifying the effect substantially, although in Parkinson’s 5 year study of immediate release (IR) and controlled release (CR) LD/DDI (carbidopa) in 681 patients, ironically reported earlier in 1997, and later in 1999, in whom dosage could be adjusted up to five or more times a day resulted not only in a lower frequency of dyskinesia (20.6% IR, 21.7% CR) at 5 years but also a lower mean total daily dose (426 mg IR; 510 mg CR (bi.equivalent)).

Whereas it has been argued that different drug preparations and methods of assessment invalidate comparison, it may be simply that less frequent higher pulsatile dosage provokes not only greater dyskinesia but also, as a mirroring effect, greater off time as postsynaptic mechanisms adapt to cope with surges of dopamine and perhaps lose sensitivity to troughs. Patients seen during troughs would be liable to have their dose increased. If the interdose interval were fixed this would lead to a vicious circle.

Given reports of long term resolution of dyskinesia and on/off effects in response to various methods of slow release stimulation at an appropriate strength, including continuous daytime jejunal infusion of LD/DDI (with little or no change in LD/DDI dosage requirement over 57 months), and of a neuroprotective effect of levodopa, the results of Rascol et al should not dissuade others from pursuing oral treatment with LD/DDI in a more frequent, lower dose regime. With gradual (allowing for the long, duration action of levodopa) titration of slow release LD/DDI dosage and interval (if necessary using a timer), against response and compliance of patient (or carer), it may in theory and, with sufficient observation and titration, in practice be possible to approximate to such a steady state titration of response. This would have potentially less risk for developing hallucinations, and would cost less.

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Brooks replies: Ponsford seems to focus primarily on the design and findings of the 056 trial of ropinirole versus levodopa in early Parkinson’s disease recently reported in the N Engl J Med rather than the editorial as a whole; however, to take up his points:

Firstly, he suggests that it is unfortunate that the 056 trial required a three times daily levodopa dosage regime as use of more frequent smaller doses could have reduced the incidence of dyskinia. Whereas it has been argued that a three times daily regime in part to match the three times daily regime of ropinirole also because it was thought that this regime reflected common clinical practice in patients with early Parkinson’s disease, merely comparing use of multiple low doses of levodopa versus a three times daily medium dose regime in early Parkinson’s disease would, however, be of great interest. It might well be that the multiple low dose approach in early disease would spare complications but this has yet to be shown. Addition of a catechol-O-methyltransferase inhibitor to slow release levodopa might increase the use of this regime in early Parkinson’s disease might also prove beneficial. Secondly, he suggests that the allowed presence of selegeline may have magnified the tendency of levodopa to cause complications. This could indeed be the case although stratifying for selegeline usage in the levodopa arm did not highlight any such effect.

Thirdly, he suggests that allowing the use of slow release levodopa preparations in early Parkinson’s disease could have been beneficial. There is currently no trial data to support this viewpoint; on the contrary, early use of levodopa in Parkinson’s disease recently reported has been associated with a similar prevalence of complications as the use of standard preparations.

My current feeling is that early use of dopamine agonists in suitable patients with Parkinson’s disease remains a reasonable strategy to delay complications. It may well be that in the future, however, a more optimal way of delivering levodopa is devised which achieves continuous and unbroken dopaminergic stimulation and so reduces the prevalence of fluctuations and dyskinesias.
Does disturbed homocysteine and folate metabolism in depression result from enhanced oxidative stress?

In their recent article, Bottiglieri et al described increased homocysteine concomitant with decreased folate concentrations in a subgroup of patients with depression. In addition, some relation between reduced folate availability and disturbed monoamine metabolism was found. The close relation between increased homocysteine and reduced folate concentrations, which was described previously in other clinical conditions such as cardiovascular and cerebrovascular diseases is usually ascribed to a reduced dietary intake of folate, and dietary supplementation with folate is capable of reducing hyperhomocysteinaemia.

The coincidence described of disturbed homocysteine and monoamine metabolism may shed some additional light to the possible mechanisms underlying this metabolic abnormality. Both metabolic pathways depend on the presence of reduced pteridine species: (1) the biosynthesis of methionine requires supply of methyl groups from methyl-5,6,7,8-tetrahydrofolic acid, deficiency of which results in hyperhomocysteaemia; (2) biosynthesis of serotonin, dopamine, and noradrenaline (norepinephrine) depends on the presence of 5,6,7,8-tetrahydrobiopterin, deficiency of which thus results in monoamine deficiency. Both tetrahydropteridines are recycled by dihydropyridine reductases; both compounds have strong reducing capacities and are thus rapidly oxidised by oxidising chemicals. Interestingly, recent studies show that depression is associated with activation of the immune system, and it is even speculated that an infectious agent might be involved. Immune system activation is accompanied by an increased production of reactive species by cytotoxic cells such as activated monocytes and macrophages to achieve antimicrobial and antiviral activities. Activated human monocytes/macrophages also release increased amounts of neopterin—another pteridine derivative—which is a sensitive index for the mediation of cell mediated immune reactions in patients. Recent data also point to a new functional aspect of neopterin—namely, to enhance oxidative processes. Increased concentrations of neopterin have been described in patients with depression. This raises the question whether oxidative stress rather than insufficient dietary intake of folate is the basis of 5,6,7,8-tetrahydrofolate and also 5,6,7,8-tetrahydrobiopterin deficiency. Interesteringly, in patients with Alzheimer's dementia a similar relation has already been demonstrated: hyperhomocysteinaemia was associated with reduced folate concentrations, but also an increased degree of immunological activation could be detected in the same patients. There is good reason to think that the scenario might be similar in patients with depression, and enhanced oxidative stress due to chronic immune system activation is a major cause of the loss of reductants such as 5,6,7,8-tetrahydrofolic acid and 5,6,7,8-tetrahydrobiopterin.

We thank Widner et al for suggesting an explanation of our finding: impaired folate and monoamine metabolism in some patients with depression.

The relation between homocysteine and folate is well established, which is why we included it in our study design. We assume that simply dietary deficiency is an inadequate explanation for folate deficiency in many patients with depression as several studies have failed to confirm this. We have recently reported a fall in CSF folate with aging and this may be a factor contributing to the high incidence of folate deficiency in psychogeriatric patients, including depression and dementia. We have also reported a fall in tetrahydrobiopterin (BH4) in depression which is correlated with folate deficiency, as reflected in a fall in red cell folate, and with impaired monoamine metabolism—that is, a fall in CSF monoamine metabolites.

The mechanisms of these relations between impaired folate and monoamine metabolism remain uncertain but the suggestion that oxidative stress plays a part is speculative. We are unaware of any clinical or experimental evidence that oxidative stress leads to folate deficiency. It has been suggested that folates play a part in maintaining BH4 synthesis and that the turnover of folate and BH4 to aging requires clarification. It is also relevant that S-adenosyl-methionine, the major methyl donor in the brain which derives its methyl group from methyl folate can, like folates, increase the turnover of monoamines in the brain. This and other evidence suggests that methylation mechanisms are involved in these relations and in mood and cognitive function.

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Long term follow up after perimesencephalic subarachnoid haemorrhage

Marschik et al describe the clinical course and long term outcome of 21 patients being diagnosed as having a perimesencephalic haemorrhage. The paper raises two questions.

The first is an impression of an "emperor’s new clothes syndrome" given by the first figure of the publication. This figure shows a slice of the CT made shortly after the initial episode of headache in the patient reported to have a recurrent episode of perimesencephalic haemorrhage. The legend of the figure states that the CT shows extravasated blood in the perimesencephalic subarachnoid space, but we fail to see any blood at all. Thanks to the electronic availability of the Journal we were able to review not only the paper version of the figure, but also an enlarged version on screen. Even after enlargement no blood was seen; the slice nicely shows the tentorium adjacent to the ambient cisterns, the proximal parts of the posterior cerebral arteries, and perfectly clear cisterns and in the frontal interhemispheric and Sylvian fissures.

There are several explanations for this diagnostic mystery. Firstly, the authors may have submitted an inappropriate slice of the CT. In some patients with perimesencephalic haemorrhage, the prepontine cistern is the only site where CT shows blood. If blood was visible in the prepontine cistern in this particular patient, the authors have indeed found a patient with a perimesencephalic, non-aneurysmal haemorrhage with a recurrent haemorrhage. Given the unique character of this sequence of events, it would be fair to provide the appropriate slice to convince readers of the Journal.

Secondly, if no evidence of blood is found even in the prepontine cistern, the patient may have had a CT negative subarachnoid haemorrhage. In patients with aneurysms CT can be negative, even if performed within 12 hours after onset of the haemorrhage. But a negative CT plus a negative angiography does not add up to a diagnosis of perimesencephalic haemorrhage.

Thirdly, the patient may not have had a subarachnoid haemorrhage at all. The case report tells us that lumbar puncture was positive, but does not give details. Because...
The authors reply. We respond to some of the questions raised by Rinkel and Veltkuis on our recent publication in this Journal.1 The patient of interest presented with typical clinical signs of subarachnoid haemorrhage. He complained of sudden onset of severe headaches, irradiation into the nuchal region, and nausea. Lumbar puncture was performed and blood stained CSF was found. Centrifugation of the CSF disclosed xanthochromia of the supernatant fluid and cytology demonstrated siderophages indicating the presence of intracranial haemorrhage as no lumbar puncture was carried out earlier.2 Non-contrast enhanced CT showed blood in the ambient cisterns. These findings were interpreted as perimesencephalic subarachnoid haemorrhage in two different hospitals.

Four vessel digital subtraction cerebral angiography with multiple views was negative as was a repeated angiography 10 weeks later. A third angiography performed in the course of the second episode of haemorrhage again did not disclose any source of the bleeding, and thus the question remains unsolved. A recent publication by Canhao et al studied the prevalence of vascular risk factors in patients who had perimesencephalic subarachnoid haemorrhage.3 They found that hypertension is more prevalent among patients with perimesencephalic haemorrhage than among two control groups and that among women, smoking was more common in perimesencephalic haemorrhage. However, the medical history of our patient was not relevant, and there was no history of previous arterial hypertension.

Rinkel and Veltkuis express their concern about a high rate of persisting symptoms such as headaches, irritability, depression, and fatigability in long term follow up of our patients. They state that these findings contrast with the good quality of life found in a follow up study performed by Brilstra et al4 and that these differences require explanation.

In this study, which was cited by us as well, quality of life was measured by means of the sickness impact profile and outcome of patients with subarachnoid haemorrhage was compared with that of a reference population. Analysing the submitted data, however, significant differences towards less dysfunction in patients were only proved for the categories body care, movement, and household management. Six of the 25 patients (24%) had more dysfunctions in the category work than the reference population, and 11 patients (44%) reported a change in their headache pattern as non-specific headaches occurred more often than before the haemorrhage in 10 patients and less often than before in one patient. Two patients reported fear of reblooding. Brilstra et al concluded that patients with a perimesencephalic haemorrhage have no reduction in quality of life but had admitted "that most consequences of the perimesencephalic subarachnoid haemorrhage are found in the psychosocial domains." They relate the problems with short term memory, sleeping, fears, irritability, and nervousness with the haemorrhage itself and with the experience of being admitted leading to admission to an intensive care unit.5 These results imply that in the Dutch study as well persisting symptoms are frequent and do not contrast with our findings at all. However, the focus of our follow up study was directly on these psychosocial implications of perimesencephalic subarachnoid haemorrhage. Only 38% of our patients thought that they were fully recovered and completely well whereas 62% of the patients had residual complaints. Moreover, only 41% of the patients returned to their previous occupation whereas 53% of the patients retired from work and one man became unemployed. Thus quality of life after the haemorrhage is as discussed above4 difficult to evaluate. It becomes obvious that perimesencephalic subarachnoid haemorrhage has an enormous impact on individual patients and social life.

We agree with Rinkel and Veltkuis on the further management strategy for patients with former PMSAH. We inform the patients of the benign nature of the disease and do not impose any restrictions at all. We also reassure the patients that they can return to their daily activities they undertook before the haemorrhage.

It is supposed that in 15% to 20% of the patients with subarachnoid haemorrhage the angiogram is negative and that patients with PMSAH account for about half of these patients with angiogram negative subarachnoid haemorrhage.


**Idiopathic intracranial hypertension and anticoagulant antibodies**

The study by Kesler et al concludes with the assumption that the presence of anticoagulant antibodies against aCL-Abs) indicates a unique subgroup of patients with idiopathic intracranial hypertension. Their study does not support this view. They regard as important in this respect the fact that the three patients with aCL Abs (p<0.035) were significantly older than those without antibodies. This is not surprising when it is known that the incidence of these antibodies increases with age and may be identifiable in up to 12% of healthy people.6,7 Their control group therefore needs to be age matched. Further speculation for
this conclusion is in their statement that there may have been an occult thrombosis of the cerebral venous sinuses, a fact that I agree with as CT and MRI cannot exclude a thrombosis for certain—hence intracranial hypertension would not be the diagnosis. It is not stated how soon cerebral sinus imaging was performed after the onset of symptoms. Thirdly, the concentration of raised aCL-Ab in these patients is not very high apart from the initial measurement in patient 1. Titres less than 40 units are generally not thought to be pathological but this is quite an arbitrary figure as test systems are variable and not standardised. Fourthly, with a prevalence of aCL-Ab at 5% in Israel, the presence of these antibodies in three of 37 patients is not a significant finding (χ² p<0.45). Finally, it is an accepted view that the presence of aCL-Ab may represent an epiphenomenon due to a non-specified injury. This is supported by the incidental findings of aCL-Ab in symptom-free patients. Hence the findings cannot support the authors’ proposal that the patients with aCL-Ab form a subgroup of patients with intracranial hypertension.

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BOOK REVIEWS


The neuropathology of schizophrenia has been for a long time perhaps one of the most controversial fields of biomedical research. In the mid-1980s, the 15 years after the advent of neuroimaging, a new era of intense research, and recent developments have been cumulative and reviewed in two separate chapters. The chapter on cortical pathology reviews a new generation of quantitative microscopical studies in relation to the GABA, glutamate, and dopamine systems. The problems of these studies were revisited in a separate chapter with the conclusion that it is unlikely to be a core feature of the neuropathology of schizophrenia. A chapter examines schizophrenia from the perspective of other neurodegenerative, diseases and lesions, including those which may cause schizophrenia-like symptoms—for example, metabolic diseases, epilepsy, and psychosis in neurodegenerative disorders. These provide useful information in the differential diagnosis of schizophrenia and other diseases of the nervous system with similar symptomatology.

This is a timely book, reviewing recent developments in our understanding of the disease schizophrenia. The editors have brought together international experts in the field to produce a book with a true multidisciplinary approach. Their achievement should be congratulated. However, less praise should be bestowed on the publishing house, which has failed to invest in high quality reproductions. There is a single coloured plate of neuroimaging of MRI and PET and the black and white reproductions of the same images have not been removed.

None the less, this is a book which should be purchased by those who are interested in schizophrenia, both neuropathologists and psychiatrists.

P L LANTOS

Phenomenological and Ethical Problems in Mental Handicap. By PETER BYRNE (Pp175, £40.00). Published by Macmillan Press, Basingstoke, 2000. ISBN 0 312 23460 0.

I cannot recommend this slim monograph highly enough to anyone working with people who have the disorders of mental handicap that give rise to what we term mental handicap, mental retardation, or learning disability. It is tightly argued, well written, and thought provoking and bears reading much more than once.

Psychiatrists are still the dominant medical profession working with people with learning disability, a fact of history that has been slow to change. Lothian has recently closed its large institution, one of several in Scotland that had around 1000 beds at its peak, with ward sizes to match. It is easy to condemn this partitioning of a whole section of society; it is much more difficult to reconcile and accept the fact that they do differ in a host of ways from most people and yet at the same time they have identical moral worth to any other human being. Professor Byrne’s central tenet is that these are not mutually exclusive concepts, but can be—and must be—integrated to make philosophical sense. The other paths lead on the one hand to the concept that the labelling process has created a fictional disability, that its use is a method of social control, of maintaining power by the creation of an underclass, and this denial of intrinsic or primary disability is inherent in some of the concepts of full inclusion and normalisation. The other position, perhaps more worrying, is held by some philosophers of bioethics who would define humanity and moral worth on the ability to reason, placing people with cognitive disability in a separate domain in which it is permissible to use eugenic policies to select against them, to justify infanticide.

Byrne argues with great care against both these paths, his arguments are in some places atonal and often appear as unconnected pieces, but at the end of the day the arguments are in his hands very more coherent than those of extreme paths that are described by Professor Byrne. The 86 men who used to be herded together in one of the old wards that I inherited might not agree.

WALTER MUIR

The past few years have seen a plethora of books on multiple sclerosis. Many of these books simply decorate my bookshelf and are rarely consulted by any member of the team. Some cynics have correlated a high number of recent publications with pharmaceutical interest in the condition, but there is no doubt that many of these books are purchased by the pharmaceutical companies and are often used as marketing tools.

Each new volume, therefore, needs to justify its existence in some way. In most cases the battle is between McAlpine’s *Multiple Sclerosis* and each newcomer. Most young pretenders are unable to match McAlpine in motion. McAlpine’s book is in the context of the history, epidemiology, pathology, diagnosis, and aetiologic sections. Where this book is particularly strong and justly deserves its place on the bookshelf is in the clinical sections, most of which are very helpful.

The book is divided into eight sections, including most of the ones mentioned. Section 6 deals with symptom management and rehabilitation, including specific chapters on weakness, mobility, fatigue, spastic parese, vertigo and incoordination, neuro-ophthalmologic, paroxysmal disorders, cognitive and emotional problems, pain and disabilities, bladder dysfunction, bowel disturbance, sexual dysfunction, autonomic disorders, dysarthria, and dysphagia. These chapters are generally informative and well written by specialists in their field. I would particularly pick out excellent chapters on neuro-ophthalmic signs and symptoms, by Elliot Frohman and colleagues, a very useful section on clinical and rehabilitation outcome measures by Linda Couthard-Morris, which contains analysis of most of the commonly used measures together with examples of the forms.

The later chapters are involved with “societal issues” and are more specific to the American care system than European health care models.

There is much weaker in the earlier sections and it is here that I would reach for my trusty McAlpine. A volume such as this is an opportunity not only to review evidence, but also to interpret in a particular fashion. During this interpret—


Everything we know about structure, function, and physiology in the nervous system at the cellular level—Sir Charles Sherrington being his only serious competitor. They met only once when Sherrington hosted Cajal’s stay in London to deliver the 1894 Royal Society Croonian lectures. During the visit, Cajal was arrested as a vagrant at Cambridge railway station when visiting the provinces to receive an honorary doctorate. Cajal and Sherrington fell over themselves to praise each other. Sherrington on Cajal: “He is the greatest anatomist the nervous system has ever known . . . he solved at a stroke the direction of nerve currents in their travel through the brain and spinal cord . . . it was a step of genius to study the embryonic nervous system.”

Between 1880 and 1933, Cajal wrote 288 scientific publications including 22 monographs. Much of his work remains untranslated from the original Spanish and hence unread. But the sustained admiration for Cajal’s writings and their contemporary relevance for neuroscience is now matched by a welcome revival in publishing his works. *Textura del sistema nervioso del hombre y de los vertebrados* was published from Madrid in three volumes (1897, 1898, and 1904). It was updated by Cajal with new text and illustrations for the translation into French as *Histologie du systeme nerveux de l’homme et des vertebres* by Dr Leon Azoulay (2 volumes: 1909-11). The complete French edition was first translated into English by Neely Swanson and Larry Swanson as *Histology of the Nervous System of Man and Vertebrates* (Oxford University Press, 1995). Now the original Spanish text until 1904 by translation by Pedro Pasik and Tauba Pasik as *Texture of the Nervous System of Man and the Vertebrates*. The first of three volumes appeared in 1999; the other two are promised for 2000.

The advertising flysheet champions Cajal’s discovery of growth cones, chemoattractant substances, dendritic spines, and cortical interneurons and claims absolute authority over both the French and Spanish editions. It boasts illustrations based on original reproductions of drawings archived in the Cajal Institute in Madrid (the evidence is in the *Manual-Cajal-Madrid* stamp on many figures) with very little copied from previously published editions. Facts and citations are corrected from Cajal’s original text and authenticated against contemporary sources. In which edition should the discerning Cajal reader invest? When complete, the Springer set will cost DM850/£330/$550 compared with £150 for the two Oxford volumes. The difference is worth paying. The English-Spanish text is authentic; compare “the nervous system represents the ultimate community in the evolution of living matter, and the most complicated machinery of noblest activities that Nature has to offer” (English-Spanish) with “countless modifications during evolution have provided living things with an instrument of unparalleled complexity and remarkable functions: the nervous system, the most highly organised structure in the animal kingdom” (English-French); or “it appears that with this [chemotactic] hypothesis we have shed light into a dark cave, when in reality we have explored only the entrance, from which its imposing abyss appears even more distant and black” (English-Spanish) versus “the theory of chemotaxis we advanced . . . initially appeared to be pure conjecture with no hope of verification, although recently it has gained experimental support” (English-French).

The text is authoritative and the production lavish. Pedro and Tauba Pasik include, and readily identify, translation of material added by Cajal for the French edition between 1904 and 1909. Original Spanish figures are retained but the citations are modernised and gathered in a single section completing the English-Spanish text. The lack of an index will be put right when volume three is published. The illustrations are incomparably better in the Springer than the Oxford volume[s]. The line drawings are much more crisp; the original figures of methylene blue staining reproduce poorly as black and white (Oxford) but some of their polychromatic figures are more subtle. Volume one deals with the general principles of organisation in the nervous system and Cajal’s methods, the details of neuronal structure and the spinal cord. Volume two and three deal with the medulla and pons, cerebellum, midbrain, diencephalon including the retina, cortex, and autonomic nervous system. The original Spanish and French editions are very expensive and virtually unobtainable. For the historian, physician, or scientist who studies neuroscience, whether or not to invest in the Springer set is simply not an issue—even if you already have the Oxford set. Both books are magnificent publishing achievements . . . but
the Psalms are on course to produce the definitive English language edition of the definitive Cajal.

ALASTAIR COMPSTON


This book comprises a selection of papers taken from a world psychiatry association symposium on preventive psychiatry. Two contributors are from the United States, one from Egypt, the remainder from Europe, particularly south eastern Europe. The preface opens with a reference to an earlier World Health Organisation (WHO) report which estimated that as many as one third to one half of all mental health problems could be averted by primary preventive measures. But it went on to note that in most spheres primary prevention had been neglected due principally to a lack of awareness of available effective methods, a deficiency that the book aimed to redress. Encouraged by this introduction the reader may then hope to become acquainted with some of the strategies and methodologies of preventive psychiatry. The book is well written and written in a style that is readable and enjoyable. The book is therefore an ideal book for the departmental library. It is likely to be helpful for the junior trainee. It is therefore an ideal book for the departmental library, but I fear may prove too costly for the average surgeon in training. Two Cambridge Colleges have traditionally cherished their more valuable volumes to prevent their disappearance and I suspect this volume may require an equivalent degree of supervision to prevent it disappearing into the eager registrar’s personal bookcase.

DAVID G HARDY


Hormonal changes clearly influence brain function and certain mental disorders, such as depression, are associated with, and may even result from, disorders of the endocrine system. As normal aging is associated with varying degrees of dysregulation in the endocrine system, this book addresses the hormonal basis of mental disorders in older people, which offers the possibility of new therapeutic approaches in an ever growing aged population.


The libraries of Cambridge Colleges contain many treasures. Among the particular treasures to be found in Peterhouse College is a first edition of the Anatomical Engravings of Vesalius. This exquisite volume combines practical instruction with wonderful aesthetic pleasure in a manner that has long gone from our more pedestrian age. Although aesthetic pleasure is largely absent from our modern manuals of practical instruction, nevertheless such manuals still have a place in the training and instruction of the young surgeon. This volume will undoubtedly prove useful in that respect and indeed to some degree it follows directly in the tradition of Vesalius. It represents the distillation of a lifetime’s work of Dr Segar from Freiburg and is truly a monumental volume. It is beautifully illustrated and a pleasure to handle. The labelling is clear and the diagrams are for the most part elegantly coloured, easy to follow, and stylishly executed. For a modern instruction manual it contains nothing to lose due to the aesthetic tradition exemplified by the Vesalius.

However, all manuals of surgical anatomy have the common characteristics that they portray the most salient aspects as if every surgeon soon learns, in the vast majority of their cases the normal appearances have been distorted or obliterated by the pathology which has caused the need for the surgery in the first place. However, surgeons must also know what things ought to look like even when they are not visible when he first starts out upon his surgery. This volume illustrates the differing anatomical appearances to be encountered in various neurosurgical approaches and this methodology is particularly likely to be helpful for the junior trainee. It is therefore an ideal book for the departmental library, but I fear may prove too costly for the average surgeon in training. Two Cambridge Colleges have traditionally cherished their more valuable volumes to prevent their disappearance and I suspect this volume may require an equivalent degree of supervision to prevent it disappearing into the eager registrar’s personal bookcase.

GLINDA GILLIES


Psychiatry is a strange clinical subject. It has by far the smallest knowledge base of any of the major subspecialties yet the arguments over what should enter curricula and what should be in our postgraduate examinations are as fierce as in any other Royal College. There are major requirements—for example, to understand psychotherapy and psychological treatments. Yet as a treatment tool they still play a subordinate role in many treatments in most settings for the management of the severely mentally ill. By contrast, time and time again surveys of trainee’s needs persistently cry out for good information on psychopharmacology. In addition any teaching courses in psychopharmacology are always voraciously snapped up. Our own flawed Maudsley prescribing guidelines, which started life as a simple internal document, is thirstily sought after. Essential Psychopharmacology is the book I always wanted to write but have been soundly beaten to it by Stahl. The first edition was a finely crafted book with logically distinct sections on basic science, disease mechanisms, drug action, and drug classes. This third edition is now much improved again with copious colour illustrations and bang up to date scientific information about both active therapies and new products and their associated modes of action. As the introduction states much has changed since the publication of the first edition 4 years ago. In one sense this is a slight pitfall of the book. The second edition has been prepared in the middle of a major research boom in psychopharmacology and in its attempt to be up to date it is in danger of becoming rapidly out of date. A text book format with a fair publication lag may not be the best vehicle for an attempt to cover absolutely up to date information. Nevertheless, I think the book is near perfect as a textbook of basic pharmacology. If I were to try and improve it further, I wonder whether the author and publisher might think again about the illustrations. It is superbly illustrated but sometimes the cartoon imagery is so metaphorical that it serves occasionally to be cumbersome and lacking clarity occasionally obscuring rather than clarifying the issue.

The book strangely lacks an international feel. There is a lot of Americana (drug combos) and the contents are largely based around a United States formulary with some unfamiliar drugs as well as missing some familiar European entities. All in all though a benchmark book for modern psychopharmacology teaching.

ROBERT KERWIN

This is the second edition of Gell’s systematic approach to the neurological problems likely to be encountered in general medical practice. The book seems to be aimed at general physicians in training, and medical students. Although it also contains much to engage the interest of specialist trainees in neurology, I suspect that most of them will use a more didactic text. Its appeal to medical students may be diminished by the relative lack of illustrations; pictorial material is mainly limited to anatomical line drawings in the early sections of the book. I did not encounter a single MR or CT brain scan; an omission giving the book questionable relevance to the starting point which is fundamental to contemporary diagnosis and understanding of neurological examination which are differential diagnosis.

This second edition particularly introduces details of neurological examination which are said to be unique and unavailable elsewhere. The authors’ programme for neurological examination is highly detailed and comprehensive. It is my impression that such exhaustiverote neurological examination is falling out of favour among the early sections of the book. I did not encounter a single MR or CT brain scan; an omission giving the book questionable relevance to the starting point which is fundamental to contemporary diagnosis and understanding of neurological examination which are differential diagnosis.

One could take issue with the summary range of tests which have been chosen, particularly the value of looking for protractor drift, testing finger tapping, and testing both heel–shin coordination and tandem gait. It is my impression that such exhaustiverote neurological examination must avoid redundancy, and be rich in tests which provide unequivocal evidence of pathology. So why is funduscopic examination of the optic disc omitted from the recommended screening examination, given that it can reveal the crucial physical sign of papilloedema in a patient who might otherwise be thought to have nonspecific headache?

Each chapter starts with a set of thoughtprovoking case histories. Some of us are of the mental disposition that enjoys learning from such games, although others find it less easy to engage the interest of specialist trainees in neurology, I suspect that most of them will use a more didactic text. Its appeal to medical students may be diminished by the relative lack of illustrations; pictorial material is mainly limited to anatomical line drawings in the early sections of the book. I did not encounter a single MR or CT brain scan; an omission giving the book questionable relevance to the starting point which is fundamental to contemporary diagnosis and understanding of neurological examination which are differential diagnosis.

Secondly, in view of the many changes that occur to the nervous system as part of the aging process (especially in relation to gait), and the controversy which still exists about the relation of Parkinson's disease to age related attrition of dopaminergic neurones, it would have been useful to include a chapter aimed at assisting the clinician to distinguish age related changes in motor function from Parkinsonian diseases. Thirdly, for the medical management of the elderly. The chapters are on the whole lucidly and well written introductions to the biological principles of clinical neurotoxicology, and to the major aspects of human and veterinary neurotoxicology. The chapter on human neurotoxic disease describes disease processes by system rather than by class of compound; that on veterinary neurotoxic disease describes disease by class of toxic agent. I found the first a much more valuable approach. Despite that personal preference, these first three chapters should be required reading by any aspiring neurotoxicologist, neuropathologist, or neurologist whether scientist, clinician, or veterinarian.

The second section, about 1000 pages in length, is a comprehensive listing of several hundred substances with neurotoxic potential. At its best, this section offers mini-reviews of many neurotoxic agents—chemicals—for example, acrylamide, n-hexane—and therapeutic agents—for example, chlorpromazine. At times, however, the choice of compounds for inclusion seems confused, and cross referenced particularly successful. For example, organophosphates and sarin and related organophosphate “nerve” agents are given separate sections, both dealt with in earlier editions with no cross reference at all. More problematic is the handling of natural poisons and venoms and their respective toxic components (toxins); Venoms inoculated by biting and stinging animals and the poisons responsible for events such as paralytic shellfish poison and ciguatera are invariably complex.

The clinical syndrome reflects the combined activities of numerous toxins. There is, therefore, the possibility of defining the neurotoxic potential of either the entire venom or poison or only that of the neurotoxic toxins. Each approach has its strengths and weaknesses but in this publication the editors have used both approaches without clarity in their choices.

It is a problem which I suspect that relatively wordy basic textbook will appeal more to students and junior doctors in North America than in the United Kingdom. In the United Kingdom many seem to want shorter, more compact books. Junior staff in general medical training
paralytic shellfish poisoning, is a member of many related gonyautoxins, and interconversion is common. This is not mentioned in the entry on saxitoxins. Neither is the fact that gonyautoxins are often found in blue-green algae. These confusions could relatively easily be resolved in subsequent editions of this book by describing the neurotoxic potential of major groups of toxin, “postsynaptically active toxins of snake venoms” for example. This may seem a complaint based on the personal interests of the reviewer, but the editors clearly feel that “natural” neurotoxic agents are important.

Experimental and Clinical Neurotoxicology is an unusual book in structure, organisation, and content. But it is not easily put down. I found myself constantly moving to new sections exploring its contents much as one handles a new dictionary. It is, quite simply, a good read. This new edition will become the definitive reference for the neurotoxicologist. It is an essential component of the library of any respectable toxicology or pathology laboratory and of every neuropathologist or neurotoxicologist. I doubt we shall wait 20 years for the third edition.

J B HARRIS

CORRECTION

Schrag A, Jahanshahi M, Quinn N. What contributes to the quality of life in patients with Parkinson’s disease? J Neurol Neurosurg Psychiatry 2000; 69:308-12. The numbers given for the PDQ-39 in depressed patients (BDI>17) and non-depressed patients (BDI<18) given in table 2 (top row of data) on page 309 should read 49.8 (21.4) and 23.6 (14.3) instead of 39 (18.3) and 16.7 (11.2).
Volitional and stimulation induced neuromyotonic discharges: unusual electrophysiological pattern in acquired neuromyotonia
J BEDNARÍK and Z KADANKA

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doi: 10.1136/jnnp.70.3.406

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