LETTERS TO THE EDITOR

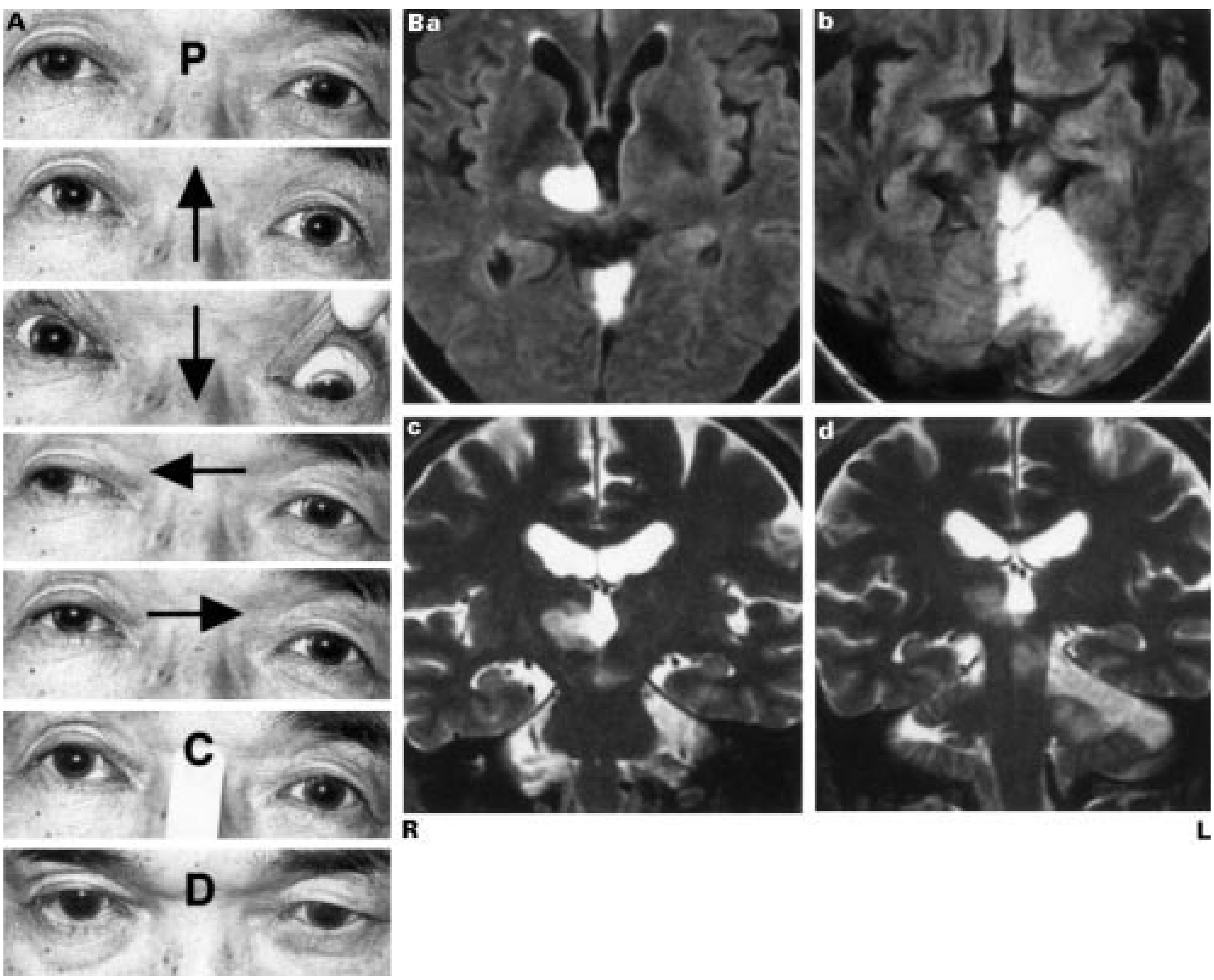
Coexisting vertical and horizontal one and a half syndromes

Supranuclear ocular movements comprise chiefly vertical and horizontal movements; horizontal movements are controlled by the subcortical centres located mainly at the pontine level and vertical movements at the level of the rostral midbrain.[1 2] The classic one and a half syndrome is produced by a unilateral pontine tegmental lesion that includes the paramedian pontine reticular formation and medial longitudinal fasciculus on the same side, and has been considered an important ocular sign in neurological diagnosis.[1 3 4] Vertical, as distinct from horizontal, one and a half syndrome, has also been documented recently.[1 2 5 6] We report on a patient with concurrent vertical and horizontal one and a half syndromes.

A 57 year old man was admitted to hospital with a sudden onset of dysarthria and loss of consciousness while playing golf. He had a history of aortic regurgitation and heart failure 8 years previously, and underwent aortic valve replacement 5 years previously, when he started to take oral antiplatelet and anticoagulant drugs. On admission, he was comatose, and his blood pressure was 140/76 mm Hg. He also had atrial fibrillation, Cheyne-Stokes respiration, bilateral miosis, and a positive Babinski's sign. Brain CT showed lesions suspected of being infarcts in the right medial thalamus and the left upper cerebellum. According to neurological findings on day 4 after onset of disease, he was in a state of hypersomnia. While awake, his head tilted slightly to the left, the right eye was slightly deviated upward, the left eye slightly downward, and there was bilateral miosis. For horizontal ocular movements, only the right eye could abduct with monocular horizontal nystagmus. Also, there was bilateral conjugated leftward palsy, indicating horizontal left one and a half syndrome. On the other hand, for vertical ocular movement, only the left eye could gaze downward. Also, difficulty in downward gaze of the right eye and bilateral conjugated upward palsy, indicating vertical one and a half syndrome, were noted (figure A). Doll's eye test (oculocephalic reflex) was weak but positive, and the eyes were unable to converge. There was also ataxic dysarthria, cerebellar ataxia of the left limbs and trunk, right sided hemisensory disturbance, and bilaterally positive Babinski's sign. Brain MRI showed infarcts in the right medial thalamus, left dorsal portion of the upper midbrain, and left upper cerebellum (figure B). On magnetic resonance angiography performed at the same time, partial obstruction of the left posterior cerebral artery was noted at its origin. Cardiogenic cerebral embolism was suspected in the pathogenesis of the serial episode in this patient.

At 7 days the patient still tended to become unconscious, accompanied by Cheyne-Stokes respiration, when talking to a familiar person. About 1 month later he talked about occurrences at the onset and began to show an interest in his surroundings. At 2 months, adduction of the left eye, bilateral leftward gaze, downward gaze of the right eye, and bilateral upward gaze showed moderate improvement. The gait disturbance persisted and he is still in a wheelchair.

Classic horizontal one and a half syndrome is commonly caused by a vascular accident



(A) Ocular movements of the patient. The right eye was slightly deviated upward, the left eye slightly downward in the primary position (P). For vertical movement, only the downward gaze of the left eye is possible. Downward palsy of the right eye and bilateral conjugated upward palsy were seen. For horizontal movements, the rightward gaze of only the right eye is present. The rightward palsy of the left eye and bilateral conjugated leftward palsy are shown. The eyes are unable to converge (C) and Doll's eye test (D) is weak but positive. (B) Brain MRI. a, b axial FLAIR imaging. c, d coronal T2 weighted imaging. High signal intensity areas are noted in the right medial thalamus, the left dorsal part of the rostral midbrain, and the left upper cerebellum.

occurring in the lower pons involving the paramedian pontine reticular formation and the medial longitudinal fasciculus.[1 3 4] In the present patient one and a half syndrome, however, was thought to be due to two concurrent lesions of distinct nerve tracts in the left upper midbrain—that is, descending fibres from the frontal eye fields of the cerebral cortex after decussation at the midbrain level and medial longitudinal fasciculus fibres ascending on the opposite side. Attention has recently focused on the rostral interstitial nucleus of the medial longitudinal fasciculus, interstitial nucleus of Cajal, and posterior commissure, all located in the tegmentum of the mesencephalon, as the brain stem centres for vertical eye movement.[1 2] Vertical one and a half syndrome consists of a bilateral conjugate upgaze palsy and a unilateral downward palsy,[2 5] or a bilateral conjugate downward palsy and a monocular upgaze palsy.[6] It has been reported that the fibres involved in upward gaze from the posterior commissure may explain bilateral upgaze palsy, and the fibres involved in downward gaze may be affected on one side before their decussation in contralateral lesion, or after their decussation in ipsilateral lesion.[2] A patient was also reported with bilateral downgaze palsy and bilateral lesions of the rostral interstitial nucleus of the medial longitudinal fasciculus.[6] Furthermore, it was reported that a unilateral lesion of the interstitial nucleus of Cajal resulted in tilting of the head towards the opposite side.[7] Therefore, it can be assumed that the leftward tilting of the head seen in the patient under study was caused by a lesion of the right interstitial nucleus of Cajal.

The present patient thus seems to be a rare case of the coexistence of two distinct syndromes, vertical and horizontal one and a half syndromes, although the lesions responsible for these syndromes are different. Even though the exact anatomical and physiological mechanism underlying vertical gaze still remains obscure in many respects, vertical one and a half syndrome is considered to be one of the important neurological signs suggestive of a lesion affecting the rostral midbrain. The particular pathogenetic mechanism of this interesting syndrome will be elucidated through future elaborate comparative studies of clinical manifestations and diagnostic imaging.

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Malignant catatonia secondary to sporadic encephalitis lethargica

Catatonia is a neuropsychiatric syndrome characterised by a combination of psychosocial withdrawal and various movement disorders. Kahlbahm first described this syndrome in 1868 when he noted this condition of "profound mental anguish". In 1893, Kraeplin limited catatonia to a subtype of dementia praecox, later redefined by Bleuler in 1906 as catatonic schizophrenia. Since then, it has become increasingly apparent that the catatonic syndrome can be seen not just in schizophrenia, but in affective disorders as well as secondary to various underlying medical conditions, leading the DSM-IV to broaden its categorisation of catatonia to include these other entities. In the early 1900s, a condition known variously as epidemic encephalitis, encephalitis lethargica, or Von Economo's disease was described, affecting more than 65 000 patients from 1919 to 1929.[1] Case descriptions reported during this time bear striking similarities to our modern definitions of catatonia. Throughout recent years, isolated cases of encephalitis lethargica have been reported.[2 3] We present a patient with features of sporadic encephalitis lethargica and discuss management of this entity in the context of catatonia.

The patient was a 22 year old previously psychologically and neurologically healthy woman who was transferred to the Barrow Neurological Institute after a 4 week stay in hospital for progressive immobility, mutism, posturing, and tremor. Initial evaluation had shown a CSF lymphocytosis, increased liver transaminases, and an EEG with bifrontal slowing. Further investigation as to aetiology of her meningoencephalitis was negative including brain MRI, brain biopsy, vasculitic profile, and comprehensive infectious disease evaluation for both endemic as well as epidemic encephalitis. An FDG-PET showed bilateral cortical hypometabolism and asymmetric thalamic hypometabolism. Over the course of her initial stay in hospital, she was intermittently agitated and chanting with frequent tremors, posturing, and occulogyric crisis. She had intermittent fever and tachycardia for which no source was found. Before her transfer, she became mute, stopped eating, and was bedridden with a percutaneous feeding tube and indwelling urinary catheter. Her initial evaluation at Barrow Neurological Institute showed her to be febrile (38.4°C) and tachycardic (130 bpm). She was mute with a staring, frightened expression and, although she seemed to attend to conversation at times, would not follow commands. Tone was diffusely increased with active resistance to passive movement of the limbs and catalepsy (waxy flexibility). She had a diffuse, asymmetric tremor, repetitive tongue thrusting, and occasional dystonic posturing of the arms. She had remarkable insensitivity to noxious stimuli, normal tendon reflexes, and flexor plantar responses. Repeat metabolic and infection evaluation was negative. Based on her history of intermittent agitation and verbigeration with progression into a mute, immobile state punctuated with random tremors, stereotypies, and abnormal tone, a diagnosis of catatonia was made. She had a brief trial of intravenous lorazepam that improved her motor symptoms but produced excessive sedation and respiratory compromise. She was then referred for electroconvulsive therapy (ECT) and had four treatments over 2 weeks with dramatic improvement in her symptoms. Repeat FDG-PET was normal. She was discharged to a rehabilitation facility and at 6 month follow up, she had made a full recovery and returned to full time employment.

The diagnosis of catatonia has not been standardised but instead relies on a range of typical clinical features that combine an alteration of behaviour with stereotypic movement disorders. Catalepsy, although considered by Bleuler to be intrinsic to the condition, is currently not considered mandatory for the diagnosis. Cardinal signs are felt to immobility, mutism, and withdrawal with secondary features including staring, rigidity, posturing or grimacing, negativism, waxy flexibility (catalepsy), echophenomenon, stereotypy, and verbigeration. Criteria have been proposed which include many of the above signs in an effort to standardise diagnosis and treatment.[4] Lethal (or malignant) catatonia has additional features of hyperthermia, autonomic instability, and rigidity often severe enough to lead to death through rhabdomyolysis, renal failure, and cardiovascular collapse.

Aetiologies of catatonia are varied and although its association with schizophrenia is accepted, it is most often seen with affective disorders. Medical conditions are increasingly becoming recognised as causes of a catatonic syndrome. When first described, encephalitis lethargica produced three relatively distinct, although often overlapping neurological syndromes.[1] The first, and most common, began with a flu-like illness that progressed with increasing sleepiness, ocular motility problems (including oculogyric crisis), and pupillary abnormalities and is known as the somnolent-ophthalmoplegic form. The parkinsonian subtype generally presented with bradykinesia, catalepsy, and mutism and most closely resembles catatonia. The final variety, recognised as the hyperkinetic form, had a more psychiatric presentation with agitation, motor restlessness, obsessional behaviour, psychosis, and dyskinesis. There are no contemporary criteria for diagnosis of encephalitis lethargica, however based on historical data, we think that our patient represents a progression of the hyperkinetic form into a more parkinsonian picture punctuated by occasional dyskinesias.

The pathological substrate for catatonia is largely unknown. When it is produced by anatomical derangement, abnormalities are most often seen in the thalamus, subthalamus, and substantia nigra. In patients dying from encephalitis lethargica, severe destructive changes were seen in the substantia nigra and, to a lesser extent, in the subthalamic nuclei and other basal ganglia structures. Our patient had a normal brain MRI and FDG-PET suggesting asymmetric thalamic hypometabolism which resolved with ECT, suggesting at least functional impairment in these anatomical areas.

Evaluation for the aetiology of catatonia is outlined in our report. Treatment is aimed at addressing any underlying medical conditions that may be producing the syndrome and once this is done, directly treating the catatonia itself. Historically, this has been varied, but recent studies suggest excellent efficacy for both high dose intravenous benzodiazepines and ECT.[5] Our patient began responding within 24 hours of her first ECT and although spontaneous recovery remains a possibility, we think that her improvement is due to ECT. Data regarding outcome in epidemic encephalitis lethargica reports a mortality up to 35% with an additional 40%–50% experiencing neurological and psychiatric sequelae.[1] Postencephalitic parkinsonism could be seen as far out as 20 years in patients who seemed to have recovered from the acute infection. Recovery in our patient has been complete without evidence for a progressive or relapsing neurological or psychiatric disorder, although follow up has been limited to 1 year.

In conclusion, catatonia may be produced by various causes, both neurological and psychiatric. Without a history of previous psychiatric impairment, aggressive investigation should be pursued for treatable medical conditions. Catatonia due to medical conditions may be successfully treated with therapies typically reserved for psychiatric indications. The clinical syndrome of encephalitis lethargica, although no longer epidemic in nature, is still sporadically seen and the underlying inflammatory cause is, as yet, unknown.

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Downbeat nystagmus from heat stroke

Downbeat nystagmus is an ocular motility disturbance that may be seen in various pathological conditions.[1] Although classically associated with structural lesions of the cervicomedullary junction or cerebellum, it can also occur in the setting of toxic insults and metabolic abnormalities.[1] Heat stroke is the most severe form of heat related illness, and is associated with multisystem organ failure. Heat stroke is infrequently associated with a cerebellar syndrome. We describe a case in which downbeat nystagmus was associated with a midline cerebellar syndrome in a patient with heat stroke, suggesting that the vermal cerebellum and vestibulocerebellum may be particularly susceptible to thermal injury.

A previously healthy 22 year old man without relevant medical history collapsed while on a 4 mile run during military basic training. Initial core body temperature was 39°C. He was incoherent and combative. Laboratory data showed increased creatine kinase, increased liver function tests, and prolonged coagulation variables. Measures to lower body temperature were initiated and he was transferred to our institution.

On arrival, core body temperature was 37°C. He was somnolent but able to follow commands. His sodium concentration was 135, potassium 3.2, calcium 7.5, magnesium 1.6, alanine transaminase (ALT) 2739, aspartate transaminase (AST) 2112, white blood count 4.2, haemoglobin 12.5, platelet count 43 000, international normalised ratio (INR) 2.9, and ammonia 33. Serological tests for HIV and RPR were negative. An ECG and chest radiograph were unremarkable.

Over the next few days, the patient's liver enzymatic activity improved. He received several transfusions to correct his thrombocytopenia and hypocoagulability. Three days after admission, the patient's family noted that his speech was slurred. The patient complained of blurred vision when reading or looking down.

Neuro-ophthalmological examination 5 days after the onset of his visual symptoms showed near visual acuity of J16 in primary gaze (secondary to oscillopsia) and J1 in upgaze. Kinetic perimetry was full in both eyes. Pupils, external examination, anterior segments, and fundi were within normal limits. Motility examination showed full ductions and versions. Vertical and horizontal saccades were hypometric. Vertical and horizontal smooth pursuit were abnormal (vertical more than horizontal), showing low pursuit gain. There was impaired suppression of the vestibulo-ocular reflex. Downbeat nystagmus was present in primary gaze, worsening in downgaze, and gaze down and laterally. This was poorly suppressed by fixation. His neurological examination showed cerebellar ataxia (truncal more than appendicular), and dysarthria.

A high quality MRI of the brain with and without contrast and with diffusion weighted imaging was performed 6 days after the onset of visual symptoms and was normal. A lumbar puncture showed normal opening pressure and normal CSF contents. Thiamine was added empirically with no effect. Magnesium was corrected to a concentration of 2.6 mg/dl, with no change in the downbeat nystagmus. The patient was discharged to a rehabilitation facility. He was lost to follow up.

Slow upward drifts and downward rapid phases characterise downbeat nystagmus. The velocity and amplitude of the rapid phases are often maximal when looking downward and laterally. Upward gaze typically dampens or eliminates downbeat nystagmus. Several mechanisms responsible for the syndrome have been proposed, including dysfunction of a neural integrator located in the brainstem, tonic imbalance in the vertical semicircular canal and ocular motor pathways, and an imbalance in the otolith-ocular reflex.[1] Experimental studies have shown that lesions of the posterior midline cerebellum can produce downbeat nystagmus. Takemori and Suzuki, for example, produced downbeat nystagmus in rhesus monkeys with bilateral floccular lesions.[2] Experimental evidence suggests that the flocculus, presumably through Purkinje cell activity, exerts an inhibitory influence on the mechanisms responsible for producing pathological nystagmus.[3] Downbeat nystagmus also can be seen with lesions of the cervicomedullary region—such as Chiari malformation or basilar invagination. It may be a manifestation of ischaemic or demyelinating disease in this region or in the cerebellum. It has also been associated with lithium toxicity, B12 and thiamine deficiencies, and hypomagnesaemia.[1]

Heat stroke is the most severe form of heat related illness. It results from a failure of thermoregulatory mechanisms, causing increase of core body temperature to extreme levels. Predisposing factors for heat stroke include lack of acclimatization, fatigue, obesity, sleep deprivation, and deconditioning. It is characterised clinically by signs and symptoms of CNS injury, core temperature greater than 39°C (107°F), and multisystem organ failure.[4] Involvement of the CNS in heat stroke may infrequently include cerebellar dysfunction. The cerebellar syndrome associated with heat stroke classically consists of both truncal and appendicular ataxia, horizontal nystagmus, and scanning dysarthria. The clinical characteristics, neuroimaging findings, and neurologic outcomes of cases published since the advent of neuroimaging are summarised in the table. All of the patients had some degree of midline cerebellar dysfunction, and all had initially normal neuroimaging studies.

Cerebellar Purkinje cells are known to be susceptible to metabolic stress, particularly hypoxic-ischaemic injury. There is evidence that the cerebellum in general, and Purkinje cells in particular, are selectively vulnerable to thermal injury. Heat shock proteins are a family of proteins that function in reparative and protective processes essential for cellular survival. Thermal injury has been shown to induce the transcription of heat shock protein in the rabbit cerebellum.[12] This may reflect an increased demand for thermal injury repair by Purkinje cells.

Our case is unique in that our patient had a midline cerebellar syndrome with downbeat nystagmus in the setting of heat stroke. Although hypomagnesaemia has been implicated as a cause of downbeat nystagmus, our patient's magnesium concentration was only slightly below normal for our laboratory. Furthermore, the syndrome persisted even after correction of his serum magnesium into the normal range. It may be that in the setting of an already compromised cerebellum, even borderline hypomagnesaemia may promote or accentuate downbeat nystagmus.

Our case provides clinical findings which are compatible with experimental data supporting localisation of downbeat nystagmus to the vestibulocerebellar region. It provides further evidence that this region may be particularly susceptible to thermal injury. The normal diffusion weighted MRI also supports the theory that cerebellar damage in heat stroke is caused by direct thermal injury, rather than a hypoxic-ischaemic insult.

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Clinical characteristics of published cases of cerebellar syndrome from heat stroke

Patient	*Year*		*Age/sex*	*Temperature (°C)*	*Cause of fever*	*Clinical syndrome*	*Initial imaging*	*Recovery*	*Follow up imaging*
1	1970	Mehta and Baker[5]	47M	42.2	Confinement in heated cell	Hypotonia, intention tremor, ataxia, dysarthria	Unknown	None	CBLR atrophy
2	1987	Yaqub *et al*[6]	50F	43.2	Exertion in heat	Nystagmus, dysarthria, ataxia	CT NL	Nearly complete 5 months	CT at 5 months CBLR atrophy
3	1983	Lefkowitz *et al*[7]	50F	42.5	NMS	Ataxia, dysmetria, hypotonia	CT NL	None	CT NL
4	1995	Manto *et al*[8]	39M	41.6	NMS	Gait ataxia	CT NL	None 1 year	CT CBLR atrophy
5	1996	Manto[9]	44F	42.1	Exertion in heat	Dysarthria	CT NL	Complete 2 weeks	CT at 3 months normal
6	1996	Manto and Topka[10]	39F	41.1	Heat stroke	Gait ataxia	MRI NL	Complete 7 days	Not done
7	1996	Manto and Topka[10]	55M	40.9	Pneumonia	Gait ataxia	MRI NL	Complete 3 days	Not done
8	1996	Manto and Topka[10]	48F	40.7	Pyelonephritis	Gait ataxia	MRI NL	Complete 5 days	Not done
9	1996	Manto and Topka[10]	47M	40.7	Pneumonia	Gait ataxia	MRI NL	Complete 10 days	Not done
10	1996	Manto and Topka[10]	60M	40.8	Erysipelas	Gait ataxia	MRI NL	Complete 6 days	Not done
11	1997	Albukrek *et al*[11]	45M	42	Exertion in heat	Nystagmus, ataxia, dysarthria	CT NL	None	MRI at 10 weeks CBLR atrophy

NMS=neuroleptic malignant syndrome; CBLR=cerebellar; NL=normal..

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Apolipoprotein E ε2 may be a risk factor for sporadic frontotemporal dementia

Frontotemporal dementia (FTD) is the second most common form of presenile dementia, after early onset Alzheimer's disease. Up to half of cases of FTD are thought to be familial, probably with an autosomal dominant mode of inheritance, some with mutations on chromosome 17. The genetics of sporadic FTD have been less studied, although several groups have examined the potential association of FTD with apolipoprotein E (APOE) ε4, with inconclusive results.[1–3]

We studied 11 patients with sporadic FTD (excluding patients with first degree relatives with dementia) in the cohort of the Oxford project to investigate memory and aging (OPTIMA). Nine of the 11 were histopathologically confirmed and the remaining two fulfilled the consensus criteria of Neary *et al*[4] (three of the first nine had also been clinically diagnosed by these criteria and all three were confirmed at necropsy); only one of the nine confirmed cases was Pick-type. Apolipoprotein E genotyping was performed, blind to diagnosis, by polymerase chain reaction methods[5] for the 11 patients with FTD (mean age at death or last examination: 65.7 years; six women) and for 136 elderly controls (mean age: 77.5 years; 77 women), without cognitive impairment and with CAMCOG scores greater than 80, from the OPTIMA cohort. An older control group was used to minimise the chance inclusion of future cases of FTD; APOE allele frequencies did not vary with age in our controls. Controls and patients were Caucasians from the Oxford region. Genotyping results are shown in the table.

Allele frequencies of APOE in cases of FTD versus controls, respectively, were: 0.32 versus 0.06 for APOE ε2, 0.64 versus 0.78 for APOE ε3, and 0.05 versus 0.16 for APOE ε4. The one Pick-type case was an APOE ε2/ε3 heterozygote. We did not have enough cases of FTD to distinguish between allele frequencies of predominantly frontal and mainly temporal cases. Control frequencies were similar to those widely reported for Caucasians. All control and FTD genotypes were in Hardy-Weinberg equilibrium. The above allele frequencies yielded odds ratios of FTD of 7.0 (95% confidence interval (95% CI) 2.5–19.5, p=0.0007) for APOE ε2, of 0.50 (p=0.18, NS) for APOE ε3, and of 0.25 (p=0.22, NS) for APOE ε4, suggesting that APOE ε2 could be a risk factor for FTD.

We examined eight previous reports[1–3 6] with APOE genotypes of cases of FTD and controls. This showed that seven of the eight had APOE ε3 odds ratios of FTD less than 1, as in our study, consistent with a protective association, whereas results for APOE ε2 and for APOE ε4 were highly varied. Frequencies of APOE ε2 in FTD ranged from zero[6] to a significant excess noted by Gustafson *et al*.[2] We suggest that these contrasting results are due to differences in diagnostic and exclusion criteria. Not all reports specified their diagnostic criteria and four of the eight were based solely on clinical diagnosis of FTD, which admits the possible inclusion of concomitant or misdiagnosed Alzheimer's disease, especially if NINCDS-ADRDA criteria are used.[7] Including cases of Alzheimer's disease would be expected to raise the APOE ε4 frequency and to lower that of APOE ε2. Perhaps more importantly, only two studies[2 3] of the eight excluded or separated familial cases.

Our suggestions, that APOE ε2 may be a risk factor for sporadic FTD and APOE ε3 might be protective, need to be investigated in a larger, probably collaborative study. Strict diagnostic and exclusion criteria should be used. We propose the inclusion only of histopathologically confirmed cases or of those fulfilling the consensus criteria of Neary *et al* 1998[4] (list 1 or 2, FTD or progressive non-fluent aphasia), strictly applied, and the exclusion of cases with first degree relatives with dementia, or with signs of parkinsonism at an early stage, or of corticobasal degeneration.

If it is indeed shown that APOE ε2, although protective against late onset Alzheimer's disease, is a risk factor for sporadic FTD, this will provide a new insight into mechanisms of risk and protection related to APOE in both diseases.

Since submitting this letter, we have read an important and relevant report by the Manchester group,[8] easily the largest and most comprehensive study to date on APOE frequencies in FTD and related disorders. The group examined 35 controls and 163 patients, including 58 with FTD without family history, and found no association of any APOE allele with FTD. Their APOE ε2 allele frequencies were 0.06 in controls, similar to ours, and 0.09 in non-familial cases of FTD. When pooling their data with ours, however, we obtained APOE ε2 frequencies of 0.12 in sporadic FTD (n=69) and 0.06 in controls (n=171). This gave an odds ratio of sporadic FTD for that allele of 2.15 (95% CI 1.1–4.2, p=0.04).

Table 1 Apolipoprotein E genotypes in sporadic frontotemporal dementia (FTD) and in elderly controls in OPTIMA

	Apolipoprotein E genotypes					
Subjects (n)	*2/2*	*2/3*	*2/4*	*3/3*	*3/4*	*4/4*
FTD (11)	—	6	1	4	—	—
Controls (136)	—	11	6	83	35	1

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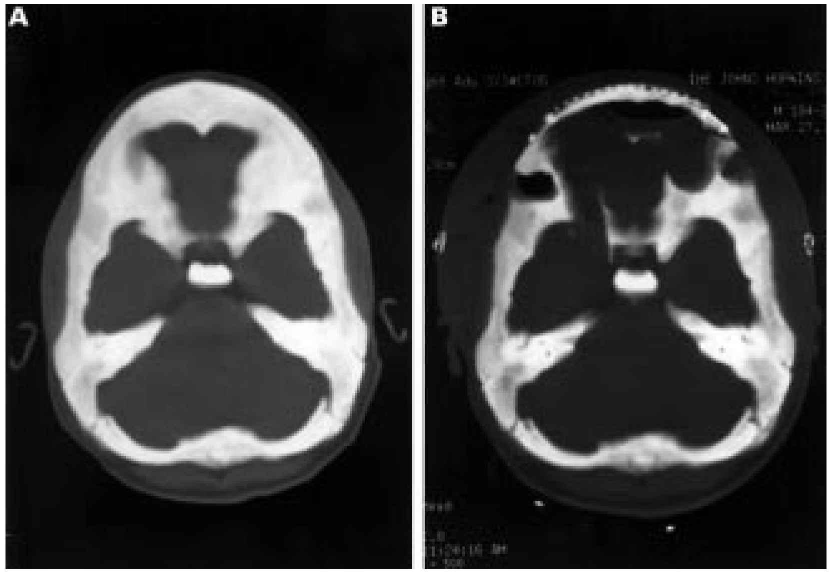
Bilateral visual improvement after unilateral optic canal decompression and cranial vault expansion in a patient with osteopetrosis, narrowed optic canals, and increased intracranial pressure

Osteopetrosis (Albers-Schonberg disease, marble bones) is a relatively rare disease that is characterised by increased skeletal mass and bone density.[1] It results from a defect in the development or function of osteoclasts with consequent impairment of bone resorption. The defect may be intrinsic to the osteoclast lineage or the mesenchymal cells that support the development and activation of the osteoclasts. Osteopetrosis is inheritable, and four clinical forms have been distinguished: autosomal-recessive malignant, autosomal-dominant benign, mild autosomal-recessive, and autosomal-recessive osteopetrosis with renal tubular acidosis. Of the four, the first two are the most prevalent.[1] The disease is characterised clinically by multiple fractures, abnormally shaped bone, and anaemia. Its neurological manifestations include cerebrovascular complications, cranial nerve palsies, papilloedema, and blindness from optic nerve atrophy.[2–5] Optic nerve atrophy is common and can result from the chronic effects of papilloedema or compression by a narrowed optic canal. Optic neuropathy associated with papilloedema can be prevented by aggressive management of intracranial pressure (ICP), whereas that associated with narrowing of the optic canal is usually treated by neurosurgical decompression.[4 5]

A 19 year old man, diagnosed with autosomal recessive osteopetrosis at about 5 months of age, presented in March 1997 with a dramatic decline in vision. He previously had had visual acuity of 20/30 in his right eye, 20/50 in his left eye, and full visual fields for most of his life. A brain CT in 1986 showed no optic canal narrowing. In 1994, he developed increased ICP and underwent a left optic nerve sheath fenestration and placement of a lumboperitoneal shunt (LPS). His vision remained normal until August of 1996 when he began to experience declining vision. He was referred to the Johns Hopkins Hospital in March of 1997.



Non-enhanced CT, axial view, with bone window settings, before and after decompression of the right optic canal and cranial vault expansion. (A) Preoperative scan shows marked thickening of the calvarium. The optic canals are narrowed by the diffusely thickened bone. (B) Postoperative scan shows that the right optic canal has been completely unroofed. Note that the decompression extends well into the orbital apex. Anterior cranial vault expansion can also be appreciated.

Visual acuity with correction was 20/200 in each eye. Near vision was 20/400 in each eye. Visual fields were limited in each eye to a tiny paracentral area of about 5 degrees. Colour vision was markedly impaired, with the patient being unable to identify any of the figures on the Hardy-Rand-Rittler (HRR) pseudoisochromatic plates. Pupils were equal and reactive to light, and there was a left relative afferent pupillary defect of 0.3 log units when measured using a neutral density filter. Extraocular movements were normal. Ophthalmoscopy disclosed bilaterally pale optic discs.

Non-contrast CT of the head showed marked diffuse thickening of the calvarium with a ground glass appearance. The bony dysplasia involved the skull base, and there was narrowing of both optic canals, the petrous carotid canals, the internal auditory canals, and the cochlear and vestibular apparatus (figure A). There was also ossification of the mastoid and frontal sinuses. The CT also showed evidence of increased ICP, including an effaced third ventricle. An indium radiotracer study showed that the LPS catheter was patent, but ultrasonography demonstrated bilateral enlargement of the retrobulbar optic nerves and a positive 30 degree test, consistent with increased ICP, and a lumbar puncture disclosed an opening pressure of 450 mm Hg, with normal CSF contents.

Consideration was given to treating the patient with acetazolamide, but because of the severity of visual loss associated with pale optic discs, and because it was unclear if his decreased visual function was caused by compression of the optic nerves by the narrowed optic canals or increased ICP, it was decided to perform bilateral non-simultaneous optic canal decompressions combined with a cranial vault expansion. A bicoronal incision was made, a full thickness scalp flap was turned down to the level of the superior orbital rims bilaterally, and a large bifrontal bone flap was removed. The roof of the right optic canal was then removed along its entire length using a high speed drill and curettes. The bone flap, which was 3 cm thick, was thinned to about 1 cm and replaced, producing a significant cranial expansion.

Four days after surgery, the patient's visual acuity had improved to 20/30 bilaterally, he could correctly identify figures on seven of 10 HRR plates with the right eye and six of 10 colour plates with the left eye, and his visual fields were markedly expanded, almost to normal. A postoperative CT confirmed complete unroofing of the right optic canal (figure B).

Osteopetrosis related visual loss is often ascribed to optic nerve compression secondary to the narrowing of the optic foramina. However, optic nerve dysfunction can also result from the effects of increased ICP. Because our patient's unilateral optic canal decompression resulted in bilateral improvement in visual acuity and visual fields, it is reasonable to conclude that increased ICP and not narrowing of the optic canals was the cause of his visual deterioration. Thus, the cranial vault expansion that was performed in addition to the unilateral optic canal decompression was responsible for the rapid and dramatic improvement in the patient's visual function.

This case provides an important lesson on the evaluation of any patient with optic neuropathy that is presumed to be secondary to narrowing of optic canals in the setting of one of the craniostenoses. Although direct compression may indeed be primarily responsible for visual deterioration in patients with osteopetrosis and related conditions, increased ICP, related to either thickening of the skull or secondary occlusion of one of the cerebral venous sinuses, should always be considered a potential aetiology, and aggressively treated when identified or suspected.

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CORRESPONDENCE

The London handicap scale

Jenkinson *et al* show that London handicap scale scores are about the same if items are weighted equally rather than using the published scale weights.[1] We reached much the same conclusion using the data from which the scale weights were derived.[2]

Handicap is defined as disadvantage in role performance due to impairments or disabilities, which implies valuation of the extent to which role performance is affected. Value—from the viewpoint of health services research—is quantified as the "utility" of a state of health. The scale weights were derived by asking various population samples to value different combinations of problems, described using the handicap dimensions and items from the handicap scale. These were analysed to determine the contribution of each of the component parts of the description.

The fact that equal weighting gives roughly the same scores as the empirically derived weights is probably because the items were carefully chosen on the basis of clinical experience to be approximately equally spaced across the range of possible severity.

Does it matter if different weighting methods lead to much the same results? Weighting processes are inexact, be they empirically derived or equal weighting, but the second approach simply increases the level of approximation. The 95% confidence intervals around the agreement between estimated and measured scores were about ± 10 (on a 0–100 scale). This measurement imprecision arises because rating health states is difficult, leading to random measurement error, and the modelling assumed that overall valuation of a state of health could be estimated by the sum of the component parts of the description, which is almost certainly an oversimplification (although goodness of fit statistics for the model were reasonable). The London handicap scale is primarily an epidemiological tool—that is, it is intended for use in groups (such as in a clinical trial). If scores are calculated for individual patients—for example, in clinical practice—there is a further approximation, that between the values and opinions of that individual, and "average" views of the population from which the values were derived. There is some evidence that the handicap dimensions have general validity, and there is some consensus on the values assigned to states of handicap. As part of the revision process of the *International Classification of Impairments, Disabilities and Handicaps*[3] qualitative studies established strong core transcultural agreement on six domains of participation with potential to be affected by health conditions, and these corresponded to the handicap dimensions (Martin Prince, personal communication). Furthermore, a comparison of values given to states of health by Hong Kong Chinese showed good agreement with those estimated by using the London handicap scale weights (derived from Londoners).[4] Neither was there convincing between population variation in scale weights assigned in the original scale development work.[2] It is not safe, however, to assume that there are no between person differences.

We are pleased to see a further independent validation of the London handicap scale. If simplification makes the scale more useful then we welcome it. The additional burden in applying the weights, however, is no more than that of adding six lines of commands in a statistical computer program (for instance, using SPSS syntax). As we have empirically derived estimates of valuations of handicap states, we see no reason why the further approximation of equal weighting is necessary.

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*Mant et al reply***:**
Whether one decides to use the original weighting scoring system of the London handicap scale or the simpler unweighted scoring system as we proposed is essentially a trade off between the advantages of each approach. As argued by Harwood and Ebrahim, the weighting system will provide what at least seems to be a more accurate estimate of the value of a health state for only limited additional analysis. However, it should be noted that weighted systems more often than not give the *appearance* of greater accuracy when in fact all they produce is *different* results.[1] Further, even if the weights are regarded as the "gold standard" the increase in accuracy is small, and there is scope for confusion (different weights have been published),[2 3] and the derivation of the score is more complex, which might lead to computational errors. However, perhaps the greatest advantage of the unweighted scoring system is that there is a simpler relation between the questionnaire responses and the final score, which makes interpretation more straightforward. There is a role for both methods of analysing the London handicap scale. Use of the simpler unweighted scoring would be likely to increase uptake and use of the instrument, without any important loss of accuracy. On the other hand, researchers who are already familiar with the weighting system have little to gain from switching to the unweighted system.

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Mass volume measurement in severe head injury

We read with interest the article by Stocchetti *et al* on the accuracy and feasibility of the ellipsoid and the Cavalieri method in assessment of the volume of intracranial mass lesions in patients with severe head injury.[1] We agree with the authors that the volume of intracranial lesions, and its change over time, is important in the diagnosis and management of patients with head injury and in the evaluation of clinical trials.[2]

However, the methodology used in the study raised our concern. We have several comments on their statements, because they are potentially misleading.

(1) The statement that computer based reading of mass lesions is the choice when accurate volume estimation is necessary, is insufficiently founded. Tracing CT lesions on a digitised screen automatically calculating area and hence volume, is a hazardous task: delineating hyperdense and hypodense lesions from normal surrounding intracranial structures cannot always be performed reliably, due to isodensity of normal brain tissue at some edges and due to partial volume effects. Moreover, lesion tracing is the same as area estimation using a simple device such as a point counting grid with sufficient grid points, and is in fact not superior at all.[3]

(2) Volume estimations based on Cavalieri's principle have to fullfill one absolute requirement: randomness.[4 5] The volume of any object may be estimated from randomised and parallel sections separated by a known distance by summing up the areas of all cross sections of the object and multiplying this sum by the known intersection distance. The total area of all cross sections may be estimated by a stereological point counting method.[3] A systematic array of grid intersection points is superimposed on each section. Giving random positioning of the test array on each section, the total number of grid intersection points hitting the object of interest affords an unbiased estimate of the

total area. In the study of Stocchetti *et al* randomness has most probably not been accounted for, as it has not been mentioned in the text and as the grid has not randomly been placed onto the CT slices.[1]

(3) When applying Cavalieri's principle it becomes mathematically possible to calculate the coefficient of error of the individual lesion mass volume. It declines in direct proportion to the total number of CT planes and to the total number of grid intersection points. Generally, a coefficient of error of less than 0.05 is obtained if the number of CT planes used is 10 or more, and the number of grid intersection points is 50 or more.[3 5] From our own practical experience we and others know that CT at standard settings (5 or 8 mm slice thickness) almost never renders sufficient sections through the lesion mass, except for very huge subdural or extradural haematomas. Spiral CT with a 3 mm section distance may overcome this problem. Another advantage of Cavalieri's principle is its applicability to any mass lesion irrespective of size and form.

(4) The average difference between the applied technique and the reference computer based value is 0.57 (SD 9.99!) ml for the Cavalieri method and 0.20 (SD 15.48!) ml for the ellipsoid method, suggesting on average acceptable agreement. However, what really matters is the accuracy, validity and reliability of the individual volume measurements. That these are not very high can be derived from the huge standard deviations of the average differences and from the considerable limits of agreement in the graphical depiction of the results.

Accuracy of the individual measurements has to be high as in the trauma coma data bank (TCDB) classification a volume of greater than 25 ml is defined as a mass lesion.[2]

(5) Although three examiners read the scans, the interobserver variability was calculated with analysis of variance (ANOVA) on the mean volumes. No intraobserver variability studies were conducted which can be considered as an omission.

(6)The TCDB CT classification being the resultant of the status of the mesencephalic cisterns, the degree of midline shift, and the presence of a mass lesion provides a ranking order of the severity of the initial injury (I=normal, II=diffuse injury, III=diffuse injury with swelling, IV=diffuse injury with shift, V=operated mass lesion, and VI=non-operated mass lesion). Intracranial mass lesion volume, although important, is but one of the measured indices in the TCDB classification. We showed recently that the TCDB CT classification system for patients with severe head injury has in fact a high interobserver and intraobserver reliability when used by clinicians without special training in neuroradiology.[6]

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Stocchetti and Colombo reply:

We are grateful to Vos *et al* for their comments. Because the main reason for our research was the fact that intracranial mass lesions are rarely measured, it is reassuring that some centres have documented expertise on such measurement.

We do not think, however, that our data, and the conclusions drawn from them, are potentially misleading, and we will try to clarify our arguments.

As indicated in the paper, we compared two pragmatic methods and a computer based method. There are, of course, limitations to each method, and tracing on the computer screen can be tricky; however, a careful tracing is feasible in expert hands and we think that the resulting calculation still gives a very acceptable reference point. If this reference method is to be questioned, an appropriate, preferably superior, method should be identified. We cannot think of any pragmatic method that would be the best choice.

Regarding the other points that aroused the concern of Vos *et al*, we agree on many and will try to clarify them.

(1) Randomness is an important prerequisite; it was not mentioned in the paper but the grid was placed on the CT slices at each reader's convenience and choice. Whether this was random enough can be debated, but it seems to ensure an adequate guarantee against systematic error.

(2) Our data did not obscure the beauties of the Cavalieri method. The direct estimator performed better than the Ellipsoid method, particularly for irregularly shaped lesions. We agree that the method performs even better with bigger lesions reconstructed using thin slices. As one of our goals was to describe feasibility, however, the comments of Vos *et al* further stress that the best can be obtained from the Cavalieri method at the price of more time and work, as we verified and reported in the paper. Counting more than 50 points in more than 10 slices adds to the precision, but seriously increases the burden of measurements.

(3) We did not base our comparison only on mean data. We share the concerns of Vos *et al* on the analysis of mean data to the extent that we have used another method, based on that of Bland and Altman. This method compares every single lesion, obtained with each method, against the corresponding reference value. The results of this detailed comparison are illustrated in figs 1 and 2 of our paper. Numerical data, summarising the analysis according to Bland and Altman, are reported in the text and table. Both in the results section and in the discussion we stated that the mean data were not able to describe the discrepancies found in single cases.

(4) Accordingly, we assessed interobserver variability by ANOVA of individual measurements, and not of the mean data. In other words, we asked whether the measurement of any specific lesion by one examiner was significantly different from the other examiners' results.[1] The ANOVA on the readings by the three examiners using the Ellipsoid method gave a p value of 0.86, and the same analysis applied to the Cavalieri direct estimator gave a p value of 0.81; we therefore concluded that this analysis excluded significant differences. It seems that the intraobserver variability was not omitted, but was in fact logically considered, and we must apologise if the text was not clear.

(5) We agree with the final paragraph of Vos *et al* on the structure of the Marshall classification, in which volume is one part of the grading. That was correctly indicated in our paper. From our experience in multicentre, international clinical trials, we are less optimistic about the proper application of the TCDB CT classification, but that is another point in favour of improving the methods for CT readings.

In conclusion we have applied a methodology that seems solid enough to substantiate our conclusion and, we hope, to fulfil the requirements of careful and competent readers.

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BOOK REVIEWS

Neurosurgery. The Scientific Basis of Clinical Practice. Third edition. Edited by CROCKARD, HAYWARD, and HOFF (two volumes, £285.00). Published by Blackwell Science, Oxford, 1999. ISBN 0632048387.

This two volume book is unique in providing a comprehensive overview of all the aspects of basic neuroscience relevant to the neurosurgeon. As such it can be regarded as an essential source of information for neurosurgical trainees around the world. The authors state in the foreword to this edition that their ambition was to "reflect in as up to date fashion as possible the expanding knowledge so essential both to trainees and established neurosurgeons alike if they are to base their clinical practice on a proper scientific basis." They can be congratulated on fulfilling their objective with such a well presented and beautifully illustrated new edition. Although clearly intended for a neurosurgical readership, there are sections that would be valuable for practitioners in other disciplines, particularly neurologists, oncologists, and orthopaedic surgeons involved in spinal surgery.

The third edition has expanded with the increased range of knowledge required by the clinical neurosurgeon. There are new and increased sections covering genetics, embryology, biomechanics, and measurement, bringing the total of chapters to 83 in 11 sections. An additional feature distinguishing it from the blue second edition is the handsome red cover, perhaps unconsciously reflecting changes in the political climate! Each chapter is very clearly laid out with an introductory outline, well structured headings, a summary, references, and a list for further reading. The manuscript is well proportioned, confining experts to present their knowledge in a concise manner in often quite short chapters. This means that the busy reader can quickly assimilate the aspects of importance.

The devotion of a section to biomechanics appears justified. The field has expanded rapidly and is a field that contains concepts with which the neurosurgeon should, at the very least, be familiar. Knowledge of how the spine responds to forces after injury and following fixation is a prerequisite to planning treatment. This has been well described, with plenty of good illustrations and radiographic images.

The chapters in the new section "Measurement and the Neurosurgeon" are welcome. They have been written in a fresh, understandable style that is kind to the reader and have been specifically targeted to the neurosurgeon. A thorough appreciation of assessment scales, outcome scores, statistical analysis, and study design is essential for those aiming to improve their management of patients by estimating the likelihood of success. Familiarity with outcome assessment is now expected not only by examiners, but is also increasingly necessary for clinical practice as doctors must justify treatments to patients and the institutions that fund healthcare.

In summary, this book is an authoritative, relevant, and comprehensive account of the scientific basis for the clinical practice of neurosurgery. It can be highly recommended not only to those preparing for an examination but also to those who might find themselves on the other side of the table.

RUPERT KETT-WHITE

Parkinson's Disease: A Self-Help Guide for Patients and Their Carers. Edited by M JAHANSHAHI and CD MARSDEN. Published by Souvenir Press, London, 1998. ISBN 0-285-63317-1.

Information is a vital tool for patients wishing to gain more control over their lives. Different sources of information will suit different patients, and this book is a useful addition to the range of available resources. Its strength comes from the authors immense clinical experience. Its weakness is that it is too hospital centred. A formidable fist of potential investigations is described (including PET). Idiopathic Parkinson's disease is described as a diagnosis of exclusion. which will certainly alarm the neuroradiologists in my health district.

Patients are given invaluable forewarning of conditions in a late 20th century British hospital: "Don't expect to be seen at the time specified on the appointment letter..."; "You may see a different doctor each time"; "The neurologist may know very little about the individual's life circumstances and about him or her as a person". Some advice about how to complain would have been invaluable. Readers are advised that "You may be presented to a large number of doctors in the course of a 'clinical presentation'": but there is no mention of multidisciplinary case conferences, home visits with a therapist, or hospital discharge planning.

The limited information about community care arrangements is dated, making no mention of care management, or of the statutory right of carers to have their own needs separately assessed. There is an invaluable and fairly comprehensive list of non-statutory resources, although much more could have been said about management of difficulties in car mobility. Oddly, wheelchairs are not in the index and get scant attention in the text. There are two unusually helpful sections on sexual dysfunction, but not enough on the management of sleep disorders. Levodopa does increase alertness in some patients, but not in others, and in my experience improved night time mobility can sometimes improve sleep. Books of this type can never suit everyone and can never be comprehensive, but there is plenty of useful and accessible information in this one. I commend it to patients and families and especially to neurologists.

CHRISTOPHER WARD

Neuroimaging, Volumes 1 and 2. Edited by WILLIAM W ORRISON JR (Pp 944 and pp 1776). Published by Harcourt International Publishers Ltd, London, 1999. ISBN 0-7216-6799-6.

The express aim of the editor of this book was to create "a master reference file on the field of neuroimaging". This may sound somewhat enigmatic, particularly as, in Europe at least, we recognise two ways of using imaging to look at the nervous system: *neuroradiology*, a clinical speciality practiced by organ specialised radiologists familiar with a wide range of techniques, closely related to the clinical neurosciences to which this journal is devoted—neurology, neurosurgery and psychiatry—and *neuroimaging*, usually the domain of physicists, psychologists, or neuroscientists expert in the application of a single technique, the impact of which on routine clinical practice has, it can be argued, often been negligible. A failure to distinguish clearly between the two markedly upsets the balance of this book.

The text is divided into four sections: history and technology (16 chapters); brain (11); head, neck, and spine (13, of which only four deal with the spine); and paediatrics (10). In each, the space devoted to some subjects seems inversely proportional to their clinical impact. Thus, in section I, the physical basis of CT and MRI merits 24 pages, with 15 references, whereas functional MRI occupies 22 pages, supported by no fewer than 154 references. Functional MRI is in vogue but, come on chaps, what about a sense of proportion? If that were not enough, two chapters on radionuclide studies (PET and SPECT respectively) have 60 pages of text between them, with 1011 references; one could be forgiven for wondering if the author had simply downloaded his Reference Manager™! I can only suppose the reason magnetic source imaging takes up 22 pages, with 117 references, must be that it is one of the editor's hobby horses.

To put things in perspective, a chapter of about 50 pages on cerebral angiography devotes 46 of those to anatomy, eight to technique, etc (of which two, on arch aortography, include the provocative statement that "the aortic arch angiogram should be evaluated before the vertebral arteries are cannulated"), and *10 lines* to indications, including the questionable statement (in the age of MRI) that intra-arterial injection should be used to detect arterial dissection. I failed to find a description of spinal angiography or its indications. Spinal arteriovenous malformations or fistulae do not appear in the index.

It would be tedious to go through the rest of the two volumes in the same way, but certain things stand out. Children's brain tumours, admittedly photogenic but usually not a source of significant diagnostic problems, occupy 80 pages (plus 651 references), while that most difficult and complex field, paediatric metabolic and endocrine disease, in which a source of definitive information, helpfully presented, would be particularly valuable for the jobbing neurologist, paediatrician, or neuroradiologist, is given rather superficial treatment in 23 pages, with 97 references. In several chapters, too many citations are of other radiology textbooks rather than of authoritative source material.

The chapter on degenerative disease of the spine, written by musculoskeletal specialists who seem to deal principally with orthopaedic surgeons or rheumatologists, is out of place in a book on neuroimaging (however defined). It deals largely with plain films, and does not address the issues germane to neurological practice; furthermore, like a number of the contributions, it omits a discussion of postoperative appearances and surgical instrumentation, essential knowledge for today's clinicians. Chapter 50, on hydrocephalus and cerebrospinal fluid dynamics, should carry a hazard warning that it presents views so personal as to be not only idiosyncratic but potentially misleading. Conversely, the chapter on the orbit and visual system, sensibly concentrating on the use of CT for the former, is admirable, apart from the caption to figure 77: the lesion described as a dermoid is almost certainly a dermolipoma.

Some 75 North American authors, few—as yet—major international figures, contributed to the 52 chapters, more than a dozen of which are the result of collaboration between at least three people. As this might lead one to expect, the literary and intellectual level, including the critical evaluation of the literature central to review-type chapters, is very variable. However, the illustrations are almost uniformly excellent and the 75 page index, included in both volumes, if also somewhat idiosyncratic, is generous. Much useful information is to be found between these hard covers, although for me the book fails to live up to the promise of the rather facetious foreword. Does it deserve a place on that already perilously overburdened departmental bookshelf? Neuroimagers will, I imagine, identify rival texts as more suited to their specially focused needs; trained neuroradiologists will indeed find much valuable reference material, but also some worrisome deficiencies and debatable notions.

IVAN MOSELEY

Prevention of Ischemic Stroke. Edited by CESARE FIESCHI and MARE FISHER (Pp 304, £65.00). Published by Martin Dunitz Publishers, London, 1999. ISBN 1-85317-738-5.

This is a multiauthor reference book with contributions from epidemiologists, neuroradiologists, neurologists, and cardiologists. It succeeds in being both comprehensive and concise, making it a valuable book to have available to "dip into". However, it is quite a long haul to read from start to finish.

There are chapters of practical use to physicians, both community and hospital based, who are involved in vascular risk factor management and specifically the primary and secondary prevention of stroke. For example, the chapter on "when to anticoagulate and at what dose" is particularly useful. Topics such as lipid lowering, antiplatelet strategies, and the management of carotid disease are covered well with pragmatic advice based on the available evidence. Where there are gaps in the evidence is also clearly stated.

There is a helpful section on haematological disorders and stroke risk with detailed information on the congenital and acquired thrombophilias and advice on routine screening for these problems. A chapter devoted to the aetiology of "young stroke" is particularly welcome. At the cellular level there is a fascinating review chapter of the molecular mechanisms affecting the development of symptomatic carotid plaques—obviously fertile ground for further research.

Contained within each chapter are helpful tables usually summarising results from available randomised controlled trials and there are some clear schematic diagrams to illustrate relevant pathophysiological and. biochemical pathways. In summary this book would be an excellent addition to any hospital or community service involved in this very important subject. It will be of value to general practitioners, physicians, cardiologists, neurologists, and trainees.

LIZ WARBURTON

The Genesis of Neuroscience. Edited by E R LAWS and GEORGE UDVARHELYI (Pp 371) Published By The American Association of Neurological Surgeons, Illinois, 1998. ISBN 1-879284-62-6.

This is an incredibly enjoyable book, which provides a fascinating insight into the history of neuroscience. It was devised by the late A Earl Walker and has been put together as a tribute to his industrious efforts to trace the history of neuroscience from ancient to modem times, and it serves as a fine tribute to him. The book builds through 11 chapters from prehistoric times through Galen and Vesalius to the founders of modem day neurology from the later part of the 19th century. The book contains endless fascinating insights into multiple aspects of neuroscience and although the illustrations are a little disappointing in parts there are some rare pictures, such as one of James Parkinson himself.

The book opens with a series of chapters which lay out the historical perspective of neuroscience, following which chapters detailing specific conditions are presented. Thus in the chapter on peripheral nerves we discover that Rollo in 1797 first described diabetic neuropathy, whereas Bontius in 1642 first described beri-beri. These chapters on regional neurology then pass on to the final chapters of the book that deal with the evolution of neurosurgery, which details in particular the first descriptions of various brain tumours. The book concludes with a chapter on the modem age of neuroscience and a magnificent list of references. If this were not enough, we are then treated to three appendices on art and neurology, medical fees, and a glossary of neurological syndromes. All most illuminating, although the account on art and neurology is not as exhaustive as it could be, given the fascinating speculations that are rife in this area. For example, what was the problem with Monet giving rise to his visual failure in later life and what, if anything, is the neurological abnormality shown in Dürer's drawing of praying hands.

This book is, though, a treasure trove of fascinating facts—for example, it was news to me that Galen was the first to describe the corpus callosum while the quadrigeminal bodies had to wait until Willis before they were acknowledged. This attention to detail and the ingenuity of these earlier investigators is inspiring, although many of these early investigators may have run into problems with local ethics committees or the Home Office inspector—for example, Galen cut the spinal cord at each level and observed the state of the animal. Indeed the industry of some of these early investigators is to be greatly admired. For example, Raymond de Vieussens de Montpelier dissected 500 fixed brains in his bid to clarify some of the finer points of neuroanatomy.

A book such as this is always going to struggle to define its audience, not least because historical medicine seems irrelevant to the high tech age of molecular genetics and functional imaging. If we can see the acetylcholine receptor at the resolution of a few Angstroms, why bother with the gross techniques of years gone by. However, there is much to admire and learn about through a knowledge of the pioneering days of neuroscience, and the elucidation of anatomical structures along with clinical conditions. It teaches much about diligence and thoughtful investigation as well as ingenuity in the face of seemingly intractable problems and scientific dogma. It is a book that is, therefore, not solely relegated to that of source material for quiz questions but reminds us of how our specialty took shape. It documents the influences that have made neurology and neurosurgery what it is today and the inspiration that has fallen on individuals over the ages and through whom we have made giant leaps in our understanding of how the brain works in health and disease. As you might have guessed by now, I loved this book and strongly recommend it to others.

ROGER BARKER

Cell Death and Diseases of the Nervous System. Edited by V E KOLIASTSOS and R R RATAN (Pp683, $145.00). Published By The Humana Press, New Jersey, 1999. ISBN 0-89603-413-5.

This book undertakes an extensive review of the fast moving field of cell death, an area of neurobiology that is currently the centre of intensive investigation both at the level of mechanisms and disease pathogenesis. The book divides into four sections that move from cellular and molecular mechanisms to animal models and human disease with possible therapeutic interventions bringing up the rear. It is thus a book that will interest both neuroscientists and neurologists alike, albeit a rather select group in each case.

The chapters are generally well written although a little sparse on illustrations, which can make some of the chapters quite daunting and intimidating. For example, the chapter on Parkinson's disease has only one figure in 12 pages of text, which tends to put all but the most dedicated reader off. In this chapter there is also evidence of some delay from the time of writing to publication as there is no real mention of the recent genetic advances in familial Parkinson's disease which should be in there given that the book was published in 1999. This is a pity given that this is currently a burgeoning field and the possible contribution of these genetic defects (for example, α-synuclein and parkin) in understanding the pathogenesis of idiopathic Parkinson's disease is a major research interest at the present time. However other chapters are more up to date; for example, the chapter on Huntington's disease discusses intranuclear inclusions even though their significance is still currently not known—do they represent a precursor to cell death or a marker of cellular neuroprotection?

Overall though the book is well presented both in terms of the topics selected and their discussion with a generally high quality of figures, including a series of rather beautiful colour plates in the middle of the book. It is therefore a book that will be a useful addition to the libraries of neurologists with an interest in neurodegenerative disorders, although other neurological conditions associated with neuronal death are touched on (for example, viral encephalitis, HIV-1 infection, trauma, and schizophrenia) which may widen its appeal. However this book will probably only ultimately interest those seeking greater neuroscientific understanding of neuronal cell loss and as such will bypass most neurologists.

ROGER BARKER