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. 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. Vertical, as distinct from horizontal, one and a half syndrome, has also been documented recently. 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.
occurring in the lowerpons involving the	paramedian pontine reticular formation and the
medial longitudinal fasciculus.1,3 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 upper left midbrain—that is, descending
fibres from the frontal eye fields of the
cerebral cortex after decussation at the
midbrain level and medial longitudinal fas-
cicull fibres ascending on the opposite side.
Attention has recently focused on the rostral
intertstitial nucleus of the medial longitudinal fas-
ciculus, interstitial nucleus of Cajal, as the
brain stem centres for vertical eye
movement.1,4 Vertical one and a half syn-
drome consists of a bilateral conjugate upgaze
palsy and a unilateral downward palsy, or a
bilateral conjugate downward palsy and a
monocular upgaze palsy.5 It has been re-
ported 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.1 A patient was also reported with bilateral
downgaze palsy and bilateral lesions on the
rostral interstitial nucleus of the medial
longitudinal fasciculus.1 Furthermore, it was
reported that a unilateral lesion of the
intertstitial nucleus of Cajal resulted in tilting
of the head towards the opposite side.1,5
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 respon-
sible for these syndromes are different. Even
though the exact anatomical and physiologi-
cal 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 mech-
nanism of this interesting syndrome will be
clarified through future elaborate compara-
tive 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 psychoso-
cial withdrawal and various movement disor-
ders. Kahlahim first described this syndrome in
1868 when he noted this condition of “pro-
found mental apathy”. Kraepelin described
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 cata-
tonic syndrome is not a true entity in schizo-
phrenia, but in affective disorders as well as
secondary to various underlying medical con-
ditions, 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 1929.6 Case
descriptions from this time bear striking similarities to our modern definitions
of catatonia. Throughout recent years, iso-
lated cases of encephalitis lethargica have
been reported, with 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,
poturing, 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 meningocerebralitis was negative
including brain MRI, laboratory, vasculitic
profile, and comprehensive infectious disease
evaluation for both endemic as well as
epidemic encephalitis. An FDG-PET showed
bilateral cortical hypometabolism and asym-
metric thalamic hypometabolism. Over the
course of her initial stay in hospital, she was
intermittently agitated and chunting with
frequent tremors, poturing, and ocular
movements. 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 ini-
tial evaluation at Barrow Neurological Insti-
tute showed her to be febrile (38°C) and
tachycardic (130 bpm). She was mute with a
staring, heightened 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, asymmet-
ic tremor, repetitive tongue thrusting, and
occasional dystonic posturing of the arms. She
had remarkable incontinence to noxious
stimuli, normal tendon reflexes, and florid
plantar responses. Repeat metabolic and infec-
tion evaluation was negative. Based on her
history of intermittent agitation and verbigeration
with progression into a mute, immobile state
punctuated with random tremors, stereotyp-
ies, 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 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. Catatyes, although
considered by Bleuler to be intrinsic to the
condition, is currently not considered man-
datory for the diagnosis. Cardinal signs are
felt to be immobility, mutism, and withdrawal
with secondary features including staring,
poturing or grimacing, negativism, waxy
flexibility (catalepsy), echophenom-
emon, stereotypy, and verbigeration. Criteria
have been proposed which include many of
the above signs in an effort to standardise
diagnosis and treatment.7 Lethal (or malig-
nant) catatonia has additional features of
hyperthermia, autonomic instability, and
rigidity often severe enough to lead to death
due to rhabdomyolysis, renal failure, and
cardiopulmonary 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 increas-
ingly becoming recognised as causes of
a catatonic syndrome. When first described,
encephalitis lethargica produced three rela-
tively distinct, although often overlapping
neurological syndromes.8 The first, and most
common, began with a flu-like illness that
progressed with increasing sleepiness, ocular
motility problems (including oculogyric cri-
is), and pupillary abnormalities and is
known as the somnolent-ophthalmoplegic form.
The parkinsonian form, often presented with
bradykinesia, catalepsy, and mutism and
tends to closely resembles catatonia.
The final variety, recognised as the hyperki-
netic form, had a more psychiatric presenta-
tion with agitation, motor restlessness, obser-
ational behaviour, psychosis, and dyskinesia.
There are no contemporary criteria for diag-
nosis of encephalitis lethargica, however
based on historical data, we think that our
case represents a progression of the hyperki-
netic 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, subthalma-
us, and substantia nigra. In patients dying
from encephalitis lethargica, severe destruc-
tive 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.¹ 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 50% experiencing neurological and psychiatric sequelae.² Post-encephalitic 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 a variety of both neurological and psychiatric. Without a history of previous psychiatric impairment, agitated agitation should be pursued for treatable medical conditions, and catatonia due to medical conditions may be best treated with these 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.


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 tonic insults and metabolic abnormalities.²,³ Heat stroke is the most severe form of heat related illness, and is associated with multisystem organ failure. Heat stroke is frequently associated with a cerebellar syndrome. We describe a patient in which downbeat nystagmus was associated with a midline cerebellar syndrome in a patient with heat stroke, suggesting that the vermis cerebellum and vestibulocerebellum may be particularly susceptible to the 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 began responding to verbal 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 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 (secondd degree) and J1 in upgaze. Kinetic perimetry was full in both eyes. Pupils, external examination, anterior segments, and fundi were within normal limits. Miotility examination showed full ductions and versions. Vertical saccades were decreased, 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 down-gaze, 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 slow 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 otolateral reflex.⑤ 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 folicular lesions.⑥ Experimentally, it suggests that the flocculus, presumably through Purkineje cell activity, exerts an inhibitory influence on the mechanisms responsible for producing pathological nystagmus.⑦ 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 elsewhere. It has also been associated with lithium toxicity, B12 and thiamine deficiencies, and hypogammaglobulinaemia.⑧

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 (102.5°F), and multisystem organ failure.⑨ 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 these 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 confer thermal and protective processes essential for cellular survival. Thermal injury has been shown to induce the transcription of heat shock protein in the rabit cerebellum.⑪ 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 hypogammaglobulinaemia 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 hypogammaglobulinaemia may promote or exacerbate 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 the cerebellum is 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

<table>
<thead>
<tr>
<th>Number</th>
<th>Year</th>
<th>Authors</th>
<th>Age (°C)</th>
<th>Hypothesis</th>
<th>Clinical Syndrome</th>
<th>Initial Imaging</th>
<th>Recovery</th>
<th>Follow Up Imaging</th>
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<tbody>
<tr>
<td>1</td>
<td>1970</td>
<td>Mehta and Baker</td>
<td>47M 42.2</td>
<td>In heat cell</td>
<td>Hypothesis</td>
<td>Unknown</td>
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<td>2</td>
<td>1987</td>
<td>Yaqub et al</td>
<td>50F 43.2</td>
<td>CBLR</td>
<td>Exertion in heat</td>
<td>CT NL</td>
<td>Nearly complete 5 months</td>
<td>CT at 5 months CBLR atrophy</td>
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<td>1983</td>
<td>Lefkowitz et al</td>
<td>50F 42.5</td>
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<td>CBLR atrophy</td>
<td>CT NL</td>
<td>None</td>
<td>CBLR atrophy</td>
</tr>
<tr>
<td>4</td>
<td>1995</td>
<td>Manto et al</td>
<td>39M 41.6</td>
<td>NMS</td>
<td>Heat stroke</td>
<td>CT NL</td>
<td>None</td>
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</tr>
<tr>
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<td>Manto</td>
<td>44F 42.1</td>
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<td>CT NL</td>
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<tr>
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<td>Manto and Topka</td>
<td>39F 41.1</td>
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<td>MRI RL</td>
<td>Complete 7 days</td>
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<td>Complete 3 days</td>
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<td>MRI RL</td>
<td>Complete 10 days</td>
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<td>MRI RL</td>
<td>Complete 6 days</td>
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<td>60M 40.8</td>
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<td>45M 42</td>
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<td>CBLR</td>
<td>MRI RL</td>
<td>None</td>
<td>MRA at 10 weeks CBLR atrophy</td>
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NMS = neuroleptic malignant syndrome; CBLR = cerebellar; NL = normal.


Apooioprotein 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 has been less studied, although several groups have examined the potential association of FTD with apolipoprotein E (APOE) ε4, with inconclusive results.1

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.3 (three of the 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. Apoipoprotein E genotyping was performed, blind to diagnosis, by polymerase chain reaction methods 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 earlier control group was used to minimize the chance of inclusion of future cases of FTD. APOE allele frequencies did not vary with age in the 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.

We examined eight previous reports1–3 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. The above frequencies yielded odds ratios of FTD of 7.0 (95% confidence interval (95% CI) 2.5–19.5, p=0.007) for APOE ε2, of 0.50 (p=0.18, NS) for APOE ε4, 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 reports1–3 of APOE genotypes of FTD versus 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 to a significant excess noted by Gustafson et al.4

We suggest that these contrasting results are due to differences in diagnostic and exclusion criteria. Not all reports specified their diagnostic criteria. Not all reports specified their diagnostic criteria. Not all reports specified their diagnostic criteria. Not all reports specified their diagnostic criteria. Not all reports specified their diagnostic criteria. Not all reports specified their diagnostic criteria. Not all reports specified their diagnostic criteria. Not all reports specified their diagnostic criteria. Not all reports specified their diagnostic criteria. Not all reports specified their diagnostic criteria. Not all reports specified their diagnostic criteria. Not all reports specified their diagnostic criteria.

We especially thank all patients and volunteers, members of OPTIMA, the Department of Neuropathology, Radiology, Dr N John, Dr S Fernandez, C Johnston, D Warden and S Latchfield. This work was supported by Bristol-Myers Squibb.

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Osteopetrosis (Albers-Schonberg disease, marble bones) is a relatively rare disease that results from a defect in bone resorption, caused by increased skeletal mass and bone density. 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. The disease is characterized clinically by multiple fractures, abnormally shaped bone, and anaemia. Its neurological manifestations include cerebrovascular complications, optic nerve palsies, papilloedema, and blindness from optic nerve atrophy. 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. A 19 year old man, diagnosed with autosomal recessive osteopetrosis at about 5 months of age, presented in March 1997 with decreased visual function caused by increased skeletal mass and bone density. He 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 orbital nerve sheath fenestration and placement of a lumbarperitoneal 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.
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. We reached much the same conclusion using the data from which the scale weights were derived. 

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, but 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, 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 agreement with those estimated by using the London handicap scale weights (derived from Londoners). 

Whether one decides to use the original scoring system as we proposed is essentially a simplification, that between the advantages of each of the component parts of the description. Approximation, which is almost certainly an oversimplification, that between the advantages of each of the component parts of the description. Approximation, which is almost certainly an oversimplification, that between the advantages of each of the component parts of the description. Approximation, which is almost certainly an oversimplification, that between the advantages of each of the component parts of the description. Approximation, which is almost certainly an oversimplification, that between the advantages of each of the component parts of the description. Approximation, which is almost certainly an oversimplification, that between the advantages of each of the component parts of the description. 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total area. In the study of Stocchetti et al random- 
ness has most probably not been ac-
counted for, as it has not been mentioned in 
the text and as the grid has not randomly 
been placed onto the CT slices.3

(3) When applying Cavaleri’s principle it becomes mathematically possible to calculate 
the coefficient of error of the individual lesion 
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 
resulted from the status of the mesencephalic 
considered as an omission.

(4) The average difference between 
the applied technique and the reference compu-
ter based value is 0.57 (SD 9.991) ml for the 
method and 0.20 (SD 15.481) ml for the elliptoid 
method, suggesting on average acceptable 
agreement. However, what really matters is the accuracy, validity and 
reliability of the individual volume measure-
ments. These are not very high can be 
deduced from huge standard deviations of 
the average differences and from the consider-
able limits of agreement in the graphical 
depiction of the results.

Accuracy of the individual measurements 
has been illustrated in the trauma com-
data bank (TCDB) classification a volume of 
greater than 25 ml is defined as a mass 
lesion.4

(5) Although three examiners read the 
slices from the observer variability was calcu-
lated with analysis of variance (ANOVA) on 
the mean volumes. No intraobserver variabil-
ity studies were conducted which can be con-
sidered 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 injury 
1=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 clas-
ification. We showed recently that the TCDB CT classification system for patients with 
severe head injury has in fact a high interob-
server and intraobserver reliability when used 
by clinicians without special training in 
neuropathology.5

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Evaluation of the Trauma Coma Data Bank 
CT Marshall classification for traumatic brain 

Stocchetti and Colombo reply:
We are grateful to Vos et al for their comments. 
Both 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, limita-
tions to each method, and tracing on the 
computer screen can be tricky; however, 
both methods are 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 prerequi-
site; 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 or not is certainly to be debated, but it 
seems to ensure an adequate guarantee against 
systematic error.

2) Our data did not obscure the beauty of the 
Cavaleri method, in which volume is one part of 
the grading. That was correctly indicated in 
our paper. From our experience in multicen-
tre, 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 

This two volume book is unique in providing 
a comprehensive overview of all the aspects of 
neurosurgery relevant to the neurosurgeon. 
As such it can be regarded as an essen-
tial 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 
esential 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 reader- 
ship, there are sections that would be valuable 
for practitioners in other disciplines, particu-
larly neurologists, oncologists, and orthopaed-
cal surgeons involved in spinal surgery.

The third edition has expanded with the 
increased range of knowledge required by the
Parkinson's Disease: A Self-Help Guide

ROSurgery. It can be highly recommended not relevant, and comprehensive account of the and the institutions that fund healthcare. As doctors must justify treatments to patients is now expected not only by examiners, but is success. Familiarity with outcome assessment patients by estimating the likelihood of changes in the political climate! Each chapter has been well described, with plenty of good illustrations and radiographic images. The chapters in the new section “Measure- ment and the Neurosurgeon” are welcome. They have been written in a fresh, understand- able style that is kind to the reader and have been specifically targeted to the neuro- surgery. It is of no great concern, and the text has been written in a fresh, under- standby style that is kind to the reader and have been specifically targeted to the neuro- surgery. It is of no great concern, and the text has been written in a fresh, under- standby style that is kind to the reader and have been specifically targeted to the neuro- surgery. It is of no great concern, and the text has been written in a fresh, under- standby style that is kind to the reader and have been specifically targeted to the neuro- surgery. It is of no great concern, and the text has been written in a fresh, under- standby style that is kind to the reader and have been specifically targeted to the neuro- surgery. It is of no great concern, and the text has been written in a fresh, under- standby style that is kind to the reader and have been specifically targeted to the neuro- surgery. It is of no great concern, and the text has been written in a fresh, under- standby style that is kind to the reader and have been specifically targeted to the neuro- surgery. 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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, antplatelet 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 interesting for these problems. A chapter devoted to the aetiology of “young stroke” is particularly interesting. 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


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 modern 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 modern 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 Bouliius in 1642 first described heron. 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 modern 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 on 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 the appropriate observed state of the animal. Indeed the industry of some of these early investigators is to be greatly admired. For example, Raymond de Vieussens de Montpellier 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 be a struggle to define its audience, not least because historical events are 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


This book undertakes an extensive review of the fast moving field of cell death, an area of neurobioloby 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, β-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 upon (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 neuroscience understanding of neuronal cell loss and as such will bypass most neurologists.