LETTERS TO THE EDITOR

Blockade of cholecystokinin-A receptors has no effect on dyskiniesias in Parkinson's disease

Cholecystokinin is one of the most abundant neuropeptides in the human CNS. It coexists with dopamine in ventral tegmental and substantia nigra neurons in rodents and primates, but the coexistence is less obvious in normal humans. It modulates central motor effects of dopamine through nigral or striatal cholecystokinin-A (excitatory) and cholecystokinin-B (inhibitory) receptors. The effect of the neuropeptide differs, however, depending on the animal species, the dose used, cotreatments, and site of injection.

Cholecystokinin is selectively decreased in the substantia nigra of patients with Parkinson's disease, and cholecystokinin-A antagonists have been used in hemiparkinsonian monkeys. Cholecystokinin inhibits levodopa induced dyskinesias in parkinsonian monkeys, but proglumide, a cholecystokinin antagonist, did not improve motor signs in dyskinesia free patients with Parkinson's disease. Proglumide is, however, a weak non-selective cholecystokinin antagonist. Oral SR 27897B (SR; Sanofi Recherche), a highly selective and potent cholecystokinin-A receptor antagonist, penetrates the CNS and blocks cholecystokinin potentiation of dopaminergic neurotransmission. We evaluated the potential antidyskinetic effects of oral SR in parkinsonian patients using a placebo controlled double blind study design and a single challenge of apomorphine, a test used to determine the antidyskinetic properties of associated treatments. As cholecystokinin-A antagonism may modify gastrointestinal motility, and consequently the kinetics of oral levodopa absorption, parenteral apomorphine was preferred to oral levodopa.

Nineteen patients with Parkinson's disease, who had motor fluctuations and levodopa induced dyskinesias for 6 months, were included in the study, which was approved by the local ethics committee. All patients gave written informed consent. Eighteen patients completed the study. Although patients in the placebo group tended to have a longer Parkinson's disease course, no significant difference in delay before turning on, the percentage of time in the on state, the percentage of motor fluctuations, the level of striatal cholecystokinin-A receptors. The investigator and the patients globally assessed from (0 to 5) changes in dyskinesias noticed during the study. Treatment with SR was tolerated well without marked adverse effects. One patient discontinued the study after 5 days of treatment due to severe dyskinesias and repeated falls. These problems were present before the study. Three patients (SR group two placebo group) stayed at the 1 mg dose level. Although three patients on SR and none on placebo reported an occasional increase in dyskinesias, daily levodopa induced dyskinesias were considered globally by both patients and investigators not to have been modified. The mean doses of apomorphine used for video testing were 5.0 mg (placebo group) and 4.6 mg (SR group). There was no significant difference in delay before turning on, the duration of the on state, the percentage of motor improvement, or in apomorphine induced dyskinesias between the two groups (table 1). Qualitative analysis failed to detect any differences either in the type of dyskinesias, their topography, or their timing (onset and end of dose dyskinesias, peak dose dyskinesias) before and after SR treatment. In this study, no significant changes in drug induced dyskinesias and in motor disability were found when patients with Parkinson's disease were treated with the cholecystokinin-A antagonist SR 27897B. The fact that this selective antagonist was ineffective in our study may have been for several reasons. The dose may have been below or even above the response threshold. Indeed, in rats, striatal perfusion with high concentrations of cholecystokinin induces hypolocomotion, whereas perfusion with low concentrations induces dopaminergic-like contralateral rotation. The apomorphine test model may not be sensitive enough. This seems unlikely however, as it has been used to show the antidyskinetic properties of fluoxetine, clozapine, and propranolol in small groups of patients. Furthermore, it permits the study of a wide range of dyskinesias, from dystonia to ballistic and choreic dyskinesias, which result from differential activation of dopamine receptors. Thus the absence of an effect of SR on any type of dyskinesias suggests that cholecystokinin may not modulate dopamine release at the level of striatal cholecystokinin-A receptors.

In conclusion, this is the first administration in patients of a selective cholecystokinin-A antagonist. Our results show that, at least under our experimental conditions, defective dopamine systems in parkinsonian patients are not modified by the inhibition of cholecystokinin-A receptors.

The study was promoted and financed by Sanofi-Recherche, Montpellier, France.

Table 1. Characteristics of the patients and clinical effect of the cholecystokinin antagonist SR27897, on parkinsonian motor disability and apomorphine induced dyskinesias

<table>
<thead>
<tr>
<th>Characteristics of the patients (mean (SD))</th>
<th>Placebo group (n=6)</th>
<th>SR 27897B group (n=12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>56 (8)</td>
<td>56 (10.5)</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>4/2</td>
<td>4/9</td>
</tr>
<tr>
<td>Disease duration (y)</td>
<td>17.3 (6)</td>
<td>12.5 (6)</td>
</tr>
<tr>
<td>Duration of levodopa therapy (y)</td>
<td>16 (6)</td>
<td>10.1 (6)</td>
</tr>
<tr>
<td>Daily levodopa dose (mg)</td>
<td>883 (570)</td>
<td>887 (415)</td>
</tr>
<tr>
<td>Hoehn and Yahr score (on/off)</td>
<td>2.3 (0.5)</td>
<td>3.8 (0.8)</td>
</tr>
<tr>
<td>Effect on motor disability (mean (SEM))</td>
<td>Day 1</td>
<td>Day 14</td>
</tr>
<tr>
<td>UPDRS III on state</td>
<td>52.5 (7.3)</td>
<td>57 (9.1)</td>
</tr>
<tr>
<td>Motor improvement (%)</td>
<td>61.8 (4.5)</td>
<td>67.1 (6.2)</td>
</tr>
<tr>
<td>Delay of dopamine effect (min)</td>
<td>3.4 (1.4)</td>
<td>10.0 (1.4)</td>
</tr>
<tr>
<td>Duration of the on phase (min)</td>
<td>46.7 (5.8)</td>
<td>55.7 (6.9)</td>
</tr>
<tr>
<td>Severity of the dyskinesia (score/min)*</td>
<td>3.5 (0.8)</td>
<td>3.9 (1.1)</td>
</tr>
</tbody>
</table>
| UPDRS-III=unified Parkinson’s disease rating scale, part III.
| #Difference between UPDRS off and on, divided by UPDRS off.
| *Student’s t test: no significant difference between day 1 and day 14.

The primary end point was the severity of dyskinesias/minute as evaluated by a video-aided standard procedure. The predomi- nant type of dyskinesias (dystonic, ballistic, or choreic) and its severity from 0 (no abnormal movements) to 4 (abnormal movements resulting in severe disability) were scored once a minute for 90 minutes in the four limbs, trunk, neck, and face by one scorer.* The minimal dose of apomor- phine testing induces dopaminergic-like contralateral rotation, whereas perfusion with low concentra- tions of cholecystokinin induces hypolocomo- tion, whereas perfusion with low concentra- tions induces dopaminergic-like contralateral rotation. The apomorphine test model may not be sensitive enough. This seems unlikely, however, as it has been used to show the antidyskinetic properties of fluoxetine, clozapine, and propranolol in small groups of patients. Furthermore, it permits the study of a wide range of dyskinesias, from dystonia to ballistic and choreic dyskinesias, which result from differential activation of dopamine receptors. Thus the absence of an effect of SR on any type of dyskinesias suggests that cholecystokinin may not modulate dopamine release at the level of striatal cholecystokinin-A receptors. However, as cholecystokinin-A antagonist binding has been found reduced in a model of hemiparkinsonism in the monkey, it cannot be totally excluded that the absence of effect of SR results from a reduction in the density of striatum cholecystokinin-A receptors in pa- tients with Parkinson's disease. Moreover, the dopamine agonist apomorphine acts postsynap- tically, whereas cholecystokinin might act presynaptically—for example, by modulating dopamine release. An effect of SR on dopamine release would not be detectable in the apomorphine test. Finally, cholecystokinin-A antagonist may not have been effective if the modulatory effects of cholecystokinin on dopamine tone is mediated only through cholecystokinin-B receptors. A study of cholecystokinin-B antagonists and agonists should be considered in patients with Parkinson's disease.

The study was promoted and financed by Sanofi-Recherche, Montpellier, France.

I ARNULF
M VIDAILHET
A-M BONNET
S DESCOMBES
C JAILON
I ARNULF
V AGNO
Clinical Investigation Center, Department of Neurology, UPRÉS EA 2397, and INSERM U269, Pins-Salpétrière Hospital, 47-83 Boulevard de l'Hôpital, 75651 Paris Cedex 13, France

C BRIEFEL
O RACOL
Clinical Investigation Center, Department of Clinical Pharmacology and INSERM U455, Purpan Hospital, Toulouse, France

J XIE
P POLLAK
Neurological Clinic, Department of Neurosciences and INSERM U118, Michallon Hospital, Grenoble, France

F CATTELIN
Sanofi-Recherche, Grenoble, France

Correspondence to: Dr I Arnulf isabelle.arnulf@psl.ap-hop-paris.fr

www.jnnp.com
Charles Bonnet’s syndrome: complete remission of complex visual hallucinations treated by gabapentin

Apart from damage or dysfunction of the CNS visual hallucinations may also arise from a pure peripheral pathology caused by lesions of the optical nerves or an ocular pathology as in macular degeneration, retinopathy, or cataract. This association of impaired central visual system and complex visual hallucinations in aged psychologically normal people is called Charles Bonnet’s syndrome. Typically there are no concomitant psychotic symptoms and the patient is usually only aware of the unreality of his experiences. However, despite a widespread agreement about hallmarks of the phenomenology, a universally accepted definition has not been found yet.1 Little is known about the underlying pathophysiology. A widely accepted hypothesis postulates a reduced afferent input causing a “release” with disinhibition of engrams usually remaining in the visual cortex, involving cholinergic and serotonergic pathways.2 Although often neglected or misdiagnosed in clinical practice, a peripheral visual pathology seems to be an important differential diagnosis of complex visual hallucinations. In a large series of 600 visually handicapped patients Teunisse et al. found a prevalence of Charles Bonnet’s syndrome of 11%. The occurrence of the syndrome was significantly associated with older age (>64) and a severe impairment of visual acuity (<0.3 in the best eye).3

Therapeutic options for Charles Bonnet’s syndrome still remain poor and of uncertain benefit for the individual patient. Even without any intervention in some patients the hallucinations can fade away within a few weeks or months. However, there are also many reports of a continuous course with ongoing tenacious hallucinations for up to 8 years.4 An implied decrease in visual acuity—for example, after cataract extraction—or also a deterioration can eliminate the hallucinations.5 Many of the widely used psychotropic drugs such as benzodiazepines, antidepressant drugs, or classic neuroleptic drugs have not been effective. Only a few reports exist of successful pharmacotherapy, with carbamazepin, valproate, melperone, or cisapride.6 Also, non-pharmacological strategies based on reassessment and self education can be helpful.1 For instance, some patients reported an influence of intensive thoughts. Even admission to hospital interrupted the hallucinations in some cases; however they recurred after discharge. We describe a patient with a 2 year history of Charles Bonnet’s syndrome with macular degeneration, with persistent and frequent hallucinations that have disappeared after treatment with gabapentin.

The 86 year old woman had a 2 year history of complex visual hallucinations on being admitted to our hospital. A senile macular degeneration had been diagnosed by her ophthalmologist 10 years previously. She complained of a daily and repetitive occurrence of images predominately showing human beings such as medieval women and knights in bright colours, but also torsos or isolated heads. None of the faces were familiar to her. They were of realistic size, coincided with normal perception of the external space, and mainly emerged when looking at a wall or lying supine facing the ceiling. The hallucinations were exclusively of a visual nature and static, but moved when she moved her eyes. They never occurred when her eyes were closed. She also sometimes experienced illusions of tiny homunculi strolling on the floor and climbing on her legs when she tried to step on them. Rarely, the content of the hallucinations changed while being watched—for example, from a female to a male head. The duration of the phenomena ranged from seconds to a few minutes. The patient recognised an increase in hallucinations during exhaustion or inflammatory diseases with raised temperature. A condition when the patient evoked hallucinations was using a mobile phone. A complex pattern of rhomboid shapes emerged with a short latency and faded away soon after having switched off the phone. The patient had full insight into the non-realistic nature of her experiences and was not at all distressed by them. None the less, she argued that the hallucinations sometimes interfered with perception when she was driving a car; therefore convincing her to seek therapy.

We asked the patient to report the time and content of the hallucinations throughout the day in a pretreatment diary. It showed that they were most likely to occur in the morning and in the evening. The most preva lent features were human beings, predominantly heads. Sometimes, objects such as old fashioned clocks or tombstones were described.

There was no psychiatric history. Medical history showed no diseases apart from hypertension and a severe polyarthrosis. She only irregularly took an antihypertensive medication (an angiotensin II antagonist and a diuretic) and painkillers (tilidine). Her general practitioner had prescribed Ginkgo biloba extract and pentoxifylline to treat the hallucinations, but without any effect. On admission to our hospital she was only taking homeopathic medication.

Neurological examination was normal. A dry atrophic macular degeneration was confirmed by our ophthalmologist. Visual acuity was 0.4 in the left eye and 0.6 in the right eye, without perimetric signs of scotomas. No cognitive dysfunction (mental state examination 29/30, average performance in testing alertness, and selective attention) or additional psychic symptoms could be found. Laboratory tests were normal. Her EEG and MRI showed no pathology. Cranial MRI only showed an age related circumscribed frontal atrophy but no abnormalities in the brain.

We started pharmacotherapy with gabapentin (300 mg/day). The patient reported only one hallucinatory event on each of the next 2 days. After that, the hallucinations disappeared and were confirmed by the patient 3 months later. The medication has been well tolerated without any side effects. There was no visual deterioration, confirmed by an examination by her own ophthalmologist at this time.

In our case report the complex visual hallucinations, both normal sized and “Liliputian”, accompanied by full insight as well as preserved cognitive skills without a specific brain pathology in morphological studies, fit in well with the typical clinical picture of Charles Bonnet’s syndrome. Also the increase during the morning and evening has been described reminiscent of the emergence of hypnagogic hallucinations in normal subjects. It is noteworthy that visual acuity was less impaired than usually reported in patients with Charles Bonnet’s syndrome, which emphasizes that a severe loss of vision is not a necessity in suffering this syndrome. As already mentioned, the natural course of the hallucinations differs greatly between patients with Charles Bonnet’s syndrome. It sometimes only covers a short period, with a spontaneous remission. The scarce pharmacological approach seems not to be necessary for all patients. None the less, an effective pharmacotherapy is needed for those with highly frequent and chronically ongoing hallucinations that are not responsive to pharmacological interventions and cause a considerable impairment of daily life. This reflects the situation in the patient presented, who came to our hospital to get an efficient therapy as she had a 2 year history of chronically ongoing hallucinations which had not responded to previous interventions. Facing the paucity of data in the field of therapeutic options we eventually considered gabapentin to be a likely favourable drug for treatment of Charles Bonnet’s syndrome for the following reasons:

(1) Anticonvulsant drugs in general may influence abnormal neuronal excitations caused by release mechanisms supported by two reports of an effective treatment of Charles Bonnet’s syndrome with carbamazepin and valproate.6

(2) There is a wide non-epileptic use of gabapentin as well as other anticonvulsant drugs including therapy of peripheral caused “phantom pains”, possibly having similar pathophysiology in another modality.

(3) Compared with the above mentioned drugs gabapentin seems to have fewer side effects (for example, compared with carbamazepin or neuroleptic drugs, which often cause marked sedation or cognitive impairments) and fewer interactions with comedication, providing a safer application, especially in the predominantly elderly Charles Bonnet’s syndrome population. The properties of gabapentin require less time for increasing the dosage as in many other anticonvulsant drugs and therefore can possibly shorten the period of stay in hospital. However, there are conjectures that GABA related anticonvul sant drugs may cause visual field defects, which might be of interest especially in the already visually impaired patients with Charles Bonnet’s syndrome. The exact action of gabapentin on neuronal systems has not been worked out but probably involves a chloride channel mechanism, apart from GABA.1

contrast with many reports on vagabatrin, there has not to our knowledge been substantial evidence for a causal association between visual field defects and gabapentin, although transient transitan and critical flicker fusion paradigms might be slightly influenced by the drug.14

In our patient, a well tolerated low dosage application of gabapentin coincided with a full remission of the hallucinations within 2 days after having started the medication and no relapses were reported in a follow up examination after 1 year. In the considered 2 year history of continuous daily repeated hallucinations this strongly points to a causal correlation, suggesting gabapentin to be an efficient and safe treatment for Charles Bonnet’s syndrome. This remains to be proved in a larger group of patients.

In view of the current data on Charles Bonnet’s syndrome, therapeutic approaches should be adjusted for each patient as there are possible individual inconsistencies in responsiveness to treatment.15 To that end, a broader range of potentially effective drugs would increase the options.

M PAULIG
H MENTRUP
Neurologisches Krankenhaus München, Traumateam 20, D-80804 Munich, Germany

Correspondence to: Dr M Paulig

7 Obrecht HM, Lodemann E, Engelmeier MP. Optic hallucinations in the aged with diseases of the eye. Z Genetol 1987;20:227–9. (Article in German.)
15 Anderson NE, Bude-Steffen C, Rosemblum MK, et al. Otopalin, and clonazepam, and valproate, was started in an attempt to reduce neurological symptoms, without any benefit. Immunomodulators—namely, intravenous immunoglobulin (IVIg) (0.4 g/kg, total dose (50 mg/day)—were introduced after the diagnosis of the renal lesion and after the interruption of all previous drugs, but symptoms did not significantly improve. Ablation of the renal tumour was performed about 3 weeks after the beginning of the symptomatology. The cancer was a well differentiated RCC with a papillary differentiation (T1G1N0); therefore the prognosis was excellent. In fact, tumour necrosis or diffusion at this stage of disease is very low, with a 5 year disease free survival rate of 100%. The patient’s serum did not stain cryostat sections of his unfixed tumour. Jun after removal of the tumour a slow but progressive improvement in the neurological symptoms started, beginning with an amelioration of opsoclonus, vertigo, and nausea. Eye movements became less frequent, and the intervals between each saccade becoming longer and longer, to disappear completely after 3 months. Some days after the intervention the patient began to eat and to spend a large part of the day with his eyes open. This progress allowed him to start physiotherapy. Six months after surgery the patient was completely normal and attending to his usual task.

This is the first report of an association between opsoclonus-myoclonus and renal cell tumour. We suggest that the presence of a kidney tumour must be taken into consideration every time an opsoclonus-myoclonus syndrome is seen, even in a young adult. This is essential as the early detection of such a tumour permits the removal of the mass in a very early phase, giving rise to a cure. Moreover, in our patient the surgical treatment resulted in the disappearance of the neurological symptoms, which had neither responded to strong immunosuppressive nor to any symptomatic medical therapy.

M C VIGLIANI
P LUCCHI
P POLO
R MUTANI
D SCHIPPER
Departmento de Neuroscience, Università degli Studi di Torino, Viale Cherasco 15, 10125 Torino, Italy
S DE LUCA
A DE ZAN
Department of Surgical Sciences, Section of Urology, University of Turin, Italy

Correspondence to: Dr M C Vigliani vigliani@usa.net

1 Anderson NE, Bude-Steffen C, Rosemblum MK, et al. Otopalin, and clonazepam, and valproate, was started in an attempt to reduce neurological symptoms, without any benefit. Immunomodulators—namely, intravenous immunoglobulin (IVIg) (0.4 g/kg, total dose (50 mg/day)—were introduced after the diagnosis of the renal lesion and after the interruption of all previous drugs, but symptoms did not significantly improve. Ablation of the renal tumour was performed about 3 weeks after the beginning of the symptomatology. The cancer was a well differentiated RCC with a papillary differentiation (T1G1N0); therefore the prognosis was excellent. In fact, tumour necrosis or diffusion at this stage of disease is very low, with a 5 year disease free survival rate of 100%. The patient’s serum did not stain cryostat sections of his unfixed tumour. Jun after removal of the tumour a slow but progressive improvement in the neurological symptoms started, beginning with an amelioration of opsoclonus, vertigo, and nausea. Eye movements became less frequent, and the intervals between each saccade becoming longer and longer, to disappear completely after 3 months. Some days after the intervention the patient began to eat and to spend a large part of the day with his eyes open. This progress allowed him to start physiotherapy. Six months after surgery the patient was completely normal and attending to his usual task.

This is the first report of an association between opsoclonus-myoclonus and renal cell tumour. We suggest that the presence of a kidney tumour must be taken into consideration every time an opsoclonus-myoclonus syndrome is seen, even in a young adult. This is essential as the early detection of such a tumour permits the removal of the mass in a very early phase, giving rise to a cure. Moreover, in our patient the surgical treatment resulted in the disappearance of the neurological symptoms, which had neither responded to strong immunosuppressive nor to any symptomatic medical therapy.

M C VIGLIANI
P LUCCHI
P POLO
R MUTANI
D SCHIPPER
Departmento de Neuroscience, Università degli Studi di Torino, Viale Cherasco 15, 10125 Torino, Italy
S DE LUCA
A DE ZAN
Department of Surgical Sciences, Section of Urology, University of Turin, Italy

Correspondence to: Dr M C Vigliani vigliani@usa.net

1 Anderson NE, Bude-Steffen C, Rosemblum MK, et al. Otopalin, and clonazepam, and valproate, was started in an attempt to reduce neurological symptoms, without any benefit. Immunomodulators—namely, intravenous immunoglobulin (IVIg) (0.4 g/kg, total dose (50 mg/day)—were introduced after the diagnosis of the renal lesion and after the interruption of all previous drugs, but symptoms did not significantly improve. Ablation of the renal tumour was performed about 3 weeks after the beginning of the symptomatology. The cancer was a well differentiated RCC with a papillary differentiation (T1G1N0); therefore the prognosis was excellent. In fact, tumour necrosis or diffusion at this stage of disease is very low, with a 5 year disease free survival rate of 100%. The patient’s serum did not stain cryostat sections of his unfixed tumour. Jun after removal of the tumour a slow but progressive improvement in the neurological symptoms started, beginning with an amelioration of opsoclonus, vertigo, and nausea. Eye movements became less frequent, and the intervals between each saccade becoming longer and longer, to disappear completely after 3 months. Some days after the intervention the patient began to eat and to spend a large part of the day with his eyes open. This progress allowed him to start physiotherapy. Six months after surgery the patient was completely normal and attending to his usual task.

This is the first report of an association between opsoclonus-myoclonus and renal cell tumour. We suggest that the presence of a kidney tumour must be taken into consideration every time an opsoclonus-myoclonus syndrome is seen, even in a young adult. This is essential as the early detection of such a tumour permits the removal of the mass in a very early phase, giving rise to a cure. Moreover, in our patient the surgical treatment resulted in the disappearance of the neurological symptoms, which had neither responded to strong immunosuppressive nor to any symptomatic medical therapy.
Azathioprine treatment in multiple sclerosis: pretreatment assessment of metaboliser status

Azathioprine is a cytotoxic immunosuppressant drug used widely in clinical neurology as an adjunct to steroid treatment for autoimmune and inflammatory conditions. As a result of the relatively high cost and modest benefit of the newly licensed immunomodulatory therapies in the treatment of multiple sclerosis there has been a resurgence of interest in the possible benefits of azathioprine. A meta-analysis in 1997 suggested that it was as effective as newer treatments in increasing the proportion of patients who remain free of relapse at 2 years.

The mode of action of azathioprine at the immune cell level remains unclear. It is converted rapidly in vivo to 6-mercaptopurine, which is extensively metabolised in vivo to 6-thioguanine nucleotides (6-TGN) which are thought to be responsible for the toxicity of azathioprine. Methylation catalysed by thiopurine methyltransferase (TPMT) leads to the production of 6-methylmercaptopurine. Wide variations in TPMT activity exist between patients and are determined by a common genetic polymorphism: 89% of the population have high TPMT concentrations, 11% intermediate concentrations, and 1 in 300 low or absent TPMT concentrations. A genetic polymorphism; 89% of the population show that the probability of freedom from relapse after 1 year is significantly greater in the azathioprine group, but the change in the expanded disability status scale (EDSS) was not significantly different. The authors concluded that the slight clinical benefits outweigh side effects and that it is still not possible to predict which patients are likely to benefit from treatment with azathioprine. Although studies included in the Cochrane database mention morbidity changes in blood counts.

The overview of azathioprine treatment in multiple sclerosis published as a meta-analysis in the *Lancet* in October 1991 showed that the probability of freedom from relapse during the first, second, and third year of treatment was significantly greater in those with high TPMT concentrations, 11% with intermediate concentrations, and 1 in 300 with low or absent TPMT concentrations. A meta-analysis included in any of the trials included in the meta-analysis. Individual variation in TPMT may explain the variable toxicity and treatment response with azathioprine in multiple sclerosis. In addition, knowledge of TPMT status in patients with multiple sclerosis could identify those unsuitable for azathioprine treatment and those in whom the dose could be increased to the top of the therapeutic range secure in the knowledge of a very low probability of toxicity. It has been suggested that studies using azathioprine may fail to detect a therapeutic effect due to underdosage—if TPMT is measured this can be avoided. Anticipation of azathioprine related toxicity and the tailoring of dose to the metaboliser status of individual patients might have considerable implications in routine clinical practice.

Migrainous brain stem disturbance in Norrie disease: case report

Norrie disease (or Norrie-Warburg syndrome) is a rare X linked disorder characterised by congenital blindness due to retinal hypoplasia. A third of patients may additionally have deafness and/or mental subnormality. The gene has been mapped to Xp11.4-11.3, in close proximity to the monoamine oxidase A and B (MAO-A and MAO-B) loci. We report a possible association of Norrie disease in a man who described paroxysmal attacks of deafness, slurred speech, and somnolence from his late teens. The character of the attacks, in addition to their marked response to [β] blockers, argues against the presence of the phenotypic character of the disease to include migrainous aura affecting the brain stem. A 38 year old left handed male computer consultant with Norrie disease sought neurological attention because of episodes of being unwell. He was born with no vision and atrophic eyeballs (phthisis bulbi). At the age of 18 he developed hearing loss necessitating hearing aids; after a period of time the hearing stabilised. His paroxysmal attacks began at this age, initially at a frequency of once every 4 or 5 months. During the year before neurological consultation, they increased to once every 2 or 3 weeks. They were predictably associated with stress or stress release. An attack typically began with a gradual deterioration (over a few minutes) of balance with further worsening in the hearing of his right ear, associated with a sense of fuzziness in his head. Occasionally he would experience a loud banging noise. The symptoms progressed to slurred speech, drowsiness, and almost complete deafness in the right ear. Observers described him as appearing pale and in discomfort during these episodes. The attacks could be truncated if he took a tablet or two of Praxilene (100 mg nafadroxyl oxalate) sufficiently rapidly after the onset of symptoms. Otherwise, they would pass off after a few hours sleep. He did not describe a headache at any time; there was a dislike for food during the attacks but no nausea or vomiting.

His medical history otherwise consisted of mild asthma, controlled by occasional bronchodilator inhaler use. He had a nephew with Norrie disease. There was a family history of migraine in his mother. General physical examination was normal. Neurological examination disclosed an articulate, insightful man with intact higher mental function. Both eyes were prothestic. There was mild sensorineural hearing loss, worse on the right. The remainder of the neurological examination was unremarkable.

Brain MRI was normal. Further investigation of his monoamine oxidase status (see below) with urinary catecholamine metabolites, whole blood serotonin, and CSF deficiency caused by a common genetic polymorphism; a review. *J Soc Med* 1992;45:752-6.


Table 1 Pathway of azathioprine metabolism

<table>
<thead>
<tr>
<th>Azathioprine</th>
<th>6-Mercaptopurine</th>
<th>Thiopurine methyltransferase (TPMT)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Xanthine oxidase</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6-Methyl thiopurine methyltransferase</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6-Thiouric acid</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Several active metabolites including 6-Thioguanine nucleotides</td>
</tr>
</tbody>
</table>
serotonin and dopamine metabolites was undetectable for logical reasons.

The time course, circumstances of precipitation, and positive family history suggested an acenthalic migrainous disturbance. Despite his asthma, prophylaxis with β blockers was initiated (10 mg propranolol twice a day, building up to a long acting preparation (80 mg Inderal LA once daily). On review 6 months later, he reported a marked positive effect, having had only one, relatively mild attack during the period. His asthma remained well controlled on a more regular use of inhalers.

Norrie disease is a member of a family of disorders, first described in 1880, resulting from mutations in genes occurring on the X chromosome. The gene is flanked on either side by the MAO-A and MAO-B loci.1 Point mutations in the Norrie disease gene lead to at least two other distinct clinical syndromes: familial and sporadic exudative retinopathy, and the retinopathy of prematurity.1 More complex genetic defects arising from larger mutations including the Norrie locus have also been described. Vossler et al2 described three boys with Norrie disease and a cephalalgic migrainous disturbance. Deterioration, and positive family history suggested altered concentrations of amine metabolites. This strongly implicates serotonin and dopamine metabolism in the phenotype of low normal intelligence, family with pure MAO-A deficiency who had a cephalalgic migrainous disturbance. De- 3

duction during the period. His asthma relieved having had only one, relatively mild attack during the period. His asthma remained well controlled on a more regular use of inhalers.

Norrie disease is a member of a family of disorders, first described in 1880, resulting from mutations in genes occurring on the X chromosome. The gene is flanked on either side by the MAO-A and MAO-B loci.1 Point mutations in the Norrie disease gene lead to at least two other distinct clinical syndromes: familial and sporadic exudative retinopathy, and the retinopathy of prematurity.1 More complex genetic defects arising from larger mutations including the Norrie locus have also been described. Vossler et al2 described three boys with Norrie disease and a cephalalgic migrainous disturbance. Deterioration, and positive family history suggested altered concentrations of amine metabolites. This strongly implicates serotonin and dopamine metabolism in the phenotype of low normal intelligence, family with pure MAO-A deficiency who had a cephalalgic migrainous disturbance. De-

Acute deterioration in Chiari type 1 malformation after chiropractic cervical manipulation

Type 1 Chiari malformation consists of caudal displacement of the cerebellar tonsils through the foramen magnum. It may also be associated with displacement of the medulla and hydromyelia. The natural history is variable, with most patients presenting between the 3rd to 5th decades.1 In a reported series of 71 patients, 69% presented with pain, 56% had weakness, 52% had numbness, and 40% complained of unsteadiness.3 Mohr et al4 classified patients’ presentations into four main groups: syringomyelia, paraparesis, cerebellar, and ‘raised pressure’. We describe a patient with a previously undiagnosed and untreated type 1 Chiari malformation who acutely deteriorated after chiropractic manipulation of the cervical spine.

This white woman first presented at the age of 47 years in August 1995. She had sustained a mild “whiplash” injury in April 1995, having been struck at low speed from behind while sitting in a stationary car. She developed neck pain a few days later and this became progressively more annoying over the next 2 months. She then attended for chiropractic manipulation of the neck. This included repetitive high velocity, low amplitude thrusting movements at the base of the neck. Immediately after the therapy session, her neck pain worsened, spreading to involve the occiput, vertex, and frontal head regions. It was made worse by coughing, lifting, and bending over. She became aware of diplopia and intermittent difficulties swallowing. She had progressive gait instability when walking longer distances. In retrospect, she had many years of poor balance, with difficulty walking on uneven ground when wearing high heels. There was no spasticity or sensory disturbance. Her history was unremarkable apart from total gastrectomy for a benign peptic ulcer. She was receiving regular B12 injections.

Examination showed normal visual acuity and funduscopic findings. There was bilateral horizontal gaze evoked nystagmus and mildly impaired horizontal vestibulo-ocular reflex suppression. Vertical pursuit was abnormal with markedly impaired vertical vestibulo-ocular reflex suppression. There was right hypertropia on right gaze. There was no facial weakness or sensory loss. She had a “nasal” quality to her speech, with mild dysarthria with rapid consonants. The jaw jerk was pathologically brisk. There was increased tone in the lower limbs. Deep tendon reflexes were increased with positive Hoffman’s sign and bilateral extensor plantar responses. She had a wide based gait with moderate truncal ataxia.

Plain radiographs of the neck disclosed assimilation of the posterior arch of C1 into the occiput, and abnormality of the dens. Brain MRI showed prolapse of the cerebellar tonsils through the foramen magnum to the level of the base of C2, with basilar invagination of the peg and angulation of the upper medulla (fig 1). There was mild midline cerebellar abnormality and distortion of the upper medulla. The aqueduct seemed normal. Laboratory tests disclosed compensated hypothyroidism.

She continued to deteriorate over the next 12 months, developing vertical nystagmus in the primary position, and became unable to walk unassisted.

In October 1996 she underwent a complex decompression procedure, with anterior removal of the anterior arch of C1, odontoid peg and clivus, and posterior removal of the occiput to realign the cervicomedullary junction of C1. The surgery was complicated by development of pneumonia and a loculated empyema requiring a thoracotomy for decortication, and the removal of a C1/C2 zygoaphysal joint. She required a temporary percutaneous feeding gastrostomy.

Three years after surgery she has very mild residual cerebellar ataxia, eye movement disorder, and mild dysarthria. She is able to eat a normal diet and walks independently.

Various neurological complications have been described with head and neck manipulation. Case reports have most often documented vascular injuries and stroke.1,2

The patient reported here represents a case of occult complex Chiari 1 malformation, which acutely decompressed after neck manipulation. The mechanism of injury is probably related to vigorous head rotation with direct traction on the cervical arch and compressed medulla. It is also possible that the anterior compression at the craniovertebral junction was worsened by transient subluxation of an already abnormal atlantoaxial joint.

The frequency of complications after spinal manipulation is not known, although the usual public perception is that it is relatively risk free. This patient, and the literature would suggest that there is a real, if small, complication rate with a substantial long term morbidity and disability.

Certain conditions would seem to be absolute contraindications to chiropractic manipulation, and ideally these should be identified before proceeding. Plain radiographs of the spine, with emphasis on the occipitocervical junction, have been suggested as screening tools before manipulation.1,3 If bony abnormalities or lytic changes are seen, then manipulation should be avoided. Certainly if this rule was followed, the patient would not have shown rapid deterioration. It should be emphasised however, that adult Chiari malformation is not uncommon and may not be associated with gross skeletal abnormalities.

Patients with previous symptoms of brain stem ischaemia should also avoid therapy. Others have also suggested that malignancy,
poverly controlled diabetes mellitus, anticoagulant therapy, infection, and hypermobility syndromes are absolute contraindications to spinal manipulation.1 Despite these various precautions, many potentially vulnerable patients will be unidentified and is likely that patients will continue to present with neurologic complications after chiropractic manipulation.

We are grateful to Mr Alan Crockard, National Hospital for Neurological Disease, London, UK, for performing the surgery.

W K LEONG A G KERMODE
Department of Neurology, Sir Charles Gardiner Hospital, Nedum V, Nedland, Western Australia 6069

Correspondence to: Dr A G Kermode
akermode@ozemail.com.au


Selai et al reply: We thank Sidefow and Werner for their interest in the EQ-5D and our work. They raise important points about the use and interpretation of generic quality of life instruments.

The valuation of health states raises many complex methodological and ethical issues and it is the topic of considerable debate in the literature.1 Although we have participated in this debate,1 we did not enter into a discussion of these issues in our recent paper because this was beyond the scope of that study.

The EQ-5D is a generic measure that has three distinct components, each providing separate data. The first part yields a simple descriptive profile of the respondents’ own subjective health status in five dimensions. Secondly, the respondents next rate their own health on a visual analogue scale, calibrated 0–100. Thirdly, according to how the respondents have rated themselves on the descriptive profile, a utility value can be ascertained. Thus, the EQ-5D generates a cardinal index of health, giving it considerable potential for use in both economic evaluation and for ascertaining a person’s subjective perspective of their own health status.

The EQ-5D classification system defines a fixed number of health states, which may include health states valued worse than death, but leaves open the issue of what value should be assigned to each state.1 Valuation data sets have been obtained in several countries, both European and non-European.

The evaluation of health related quality of life (HR-QOL) of patients with a given disease is generally measured using a disease specific instrument,—for example, the PDQ-39 in patients with Parkinson’s disease. As these instruments are only applicable to patients with a particular disease, they do not allow comparisons across health conditions and are of limited use in economic studies. It is therefore recommended that a generic HR-QOL instrument be used in addition to disease specific measures. The generic measure must be tested and validated before use in the respective patient population. The purpose of our study was to test the validity and feasibility of two generic measures of HR-QOL (the EQ-5D and the SF-36) in patients with Parkinson’s disease. The EQ-5D, a simple generic instrument, was shown to have good validity and feasibility and performed better than the SF-36 in this group of patients with Parkinson’s disease.

C E SELAI A SCHARG
A D SIDEROWF
Department of Neurology, University of Pennsylvania, 330 South 36th Street, Philadelphia, PA 19104, USA
Correspondence to: Dr A D Siderowf
adsiderowf@yahoo.com


Cerebral malaria

Two items in the review of cerebral malaria by Newton et al1 warrant comment. The first relates to corticosteroids in the treatment of cerebral malaria, and the second involves the definition of cerebral malaria.

The authors, citing Warrell et al2 and Hoffman et al3 stated that steroids are contraindicated in cerebral malaria because they add risks without providing any benefit.

In late December 1965, I arrived in Vietnam as a neurologist with the United States Army Medical Corps., and for the next 6 months I was the only neurologist serving United States forces in Vietnam. I was attached to the 93rd Evaluation Hospital, which opened only 2 weeks before my arrival. As recounted in a recent article about my Vietnam experience, in: Spiller B, ed. Quality of life and pharmacoeconomics in clinical trials, Philadelphia: Lippincott-Raven, 1996.

The EQ-5D—a generic quality of life measure—is a useful instrument to measure quality of life in patients with Parkinson’s disease.

We read with interest the recent article by Schrag et al,1 in which the authors showed that the EuroQol-5D (EQ-5D) is a valid measure of quality of life in patients with Parkinson’s disease. However, the authors neglected to mention two important aspects of the EQ-5D that differentiate it from typical quality of life instruments.

Firstly, the EQ-5D is a preference based measure. The summary score of the EQ-5D is calculated on a scale from 0 to 1, where 0 represents death and 1 represents perfect health. The values derived from the EQ-5D can be used to compare health states in a quantitative way. For example, a health state with a value of 0.5 is half as desirable as perfect health. The scoring rule for the EQ-5D permits scores less than 0, implying that some health states may be worse than death.

Secondly, the index scores for the EQ-5D are intended to approximate general population preferences rather than the respondent’s own health values. The EQ-5D values were developed based on ratings by a large, random sample of the adult population of the United Kingdom, The Netherlands, and Sweden.2 As a result, the summary index score does not quantify the respondent’s value of their own health, but rather the value that the general population would place on the respondent’s health. By contrast, the visual analogue scores are direct measures of the value a respondent places on their own health. It is not surprising that the summary index scores and visual analogue scores are somewhat different in the study by Schrag et al.

These properties of the EQ-5D make it an indicated measure of health status for certain applications, particularly estimating health utility for cost-utility analysis. It is, perhaps, a fortunate accident that it is also a valid measure of quality of life in patients with Parkinson’s disease.
against the use of steroids in adult patients with cerebral malaria. Given the importance of the papers in buttressing the "no steroid" mandate, I will summarise them.

Warrell et al. studied Thai patients in a village hospital. There were two groups of 50 patients each; eight in the steroid treated group died, and nine of the untreated controls died. Hoffman et al. studied Indonesians in a provincial hospital with a mean age of 10.2 years, and found that four of 19 patients treated with steroids died, and none in the untreated controls died. Hoffman at al. treated United States in a provincial hospital with a mean age of 8.6 years, and found that four of 19 patients treated with steroids died, and none in the untreated controls died. Hoffman et al. commented about the low definition of cerebral malaria in the literature, often without evidence that confounding secondary causes of enccephalopathy were excluded. We are confident that this criticism is not applicable in our series, nor others emanating from the medical experience among United States forces in Vietnam. Nevertheless, Newby et al. diagnosed cerebral malaria according to the definition of cerebral malaria, requiring "a deep level of unconsciousness" or coma. Such restricted criteria might be justified in studies comparing treatment protocols, but to insist that a cerebral condition lacks degrees of severity is contrary to the experience of any neurologist. The all or none definition of cerebral malaria is simply not acceptable.

R B DAROFF
University Hospitals of Cleveland, 11100 Euclid Avenue, Cleveland, Ohio 44106-6133, USA
rbd2@po.cwru.edu


White and Newton reply:
Daroff has queried the World Health Organisation (WHO) definition of cerebral malaria that we quoted in our paper.1 We pointed out that a patient with falciparum malaria with an impairment of consciousness or other sign of cerebral dysfunction should be treated as a medical emergency with parenteral antimalarial drugs. The point about the definition proposed by WHO,2 is to allow a direct comparison between studies in which the clinical syndromes are precisely defined.

This point is well illustrated by Dr Daroff's comments on studies of corticosteroids in malaria; he compares his studies on cerebral malaria, in which the cerebral involvement was described in terms of "extreme lethargy", "delirium", or "stupor"3 to those in whom cerebral malaria was strictly defined.4 It is difficult to compare the mortality in such disparate groups.

As for the continued use of corticosteroids in cerebral malaria, Daroff's recommendation is based on anecdotal experience during the second world war and Vietnam in the 1960s. There is little theoretical basis for using corticosteroids.5 The two double blind, randomised control trials of dexamethasone failed to demonstrate any benefit from corticosteroids in adults with a precise definition of cerebral malaria.6 Indeed the studies were associated with a significant increase in gastrointestinal bleeding,7 infections, and duration of unconsciousness.8 It is difficult to assess historical anecdotal evidence as there are many factors which may contribute, such as differences in the definitions of the clinical syndrome, drug resistance, and patient groups. Although the two randomised trials do not exclude a potential benefit, there is little substantial evidence to support the use. The onus is on the people who think that corticosteroids are beneficial, to provide more substantial data to support their conjecture, preferably as the results of a randomised trial.

C R J C NEWTON
Neurosciences Unit, The Welwyn Centre, Institute of Child Health, Makenchack Square, London WC1N 2AF UK

Correspondence to: Dr C R J C Newton
cnewton@kilifi.mimcom.net


Treatment of paroxysmal sympathetic storm with labetalol
Do et al. present a patient with paroxysmal sympathetic storm, and include a sample of the patient's ictal EEG recording.7 It is stated that the absence of clear epileptiform activity serves as evidence against these episodes being epileptic in nature. However, if indeed the EEG recordings during an attack show significant slowing, as depicted in the EEG sample, this EEG change from a presumably normal EEG background rhythm at other times, would rather indicate that these events are, indeed, of seizure origin.

Deep seated epileptic foci very often do not project any sharply configured waveforms to the scalp surface; neither do they provide reliable localising information and can appear rather in a generalised fashion. It might be suggested, that perhaps any reproducible and reliably observable EEG changes from the background rhythm that coincide with the clinical event are typically interpreted as evidence in favour of epileptiform activity. Possible candidates for surgical treatment of their epilepsy would be further investigated with implanted electrodes in an effort to obtain EEG recordings from the closest vicinity of the presumed focus. This is obviously not a justifiable approach in this patient as surgical resection is not an option in this location.

Neither should successful treatment of specific symptoms during an attack with medication other that antiepileptic drugs necessarily be interpreted as evidence against the event being epileptic. In this case report, the patient's autonomic disturbances during the episode did respond to labetolol; however, this does not necessarily exclude a possibly epileptic origin as labetolol could only have obscured the clinically observable manifestations.

O BERNATH
Aisintron Morley's Hospital, Department of Neurology, Cape Hill, Wimpole, London SW20 0DD, UK
We appreciate Bernath's thoughtful comments concerning our case report of using labetolol to treat paroxysmal sympathetic storm. We agree that ictal EEG patterns can be quite variable and subtle, and that paroxysmal slowing can correspond to a seizure even without observable sharp waves or spikes. In this context, rhythmicity is generally viewed as a major characteristic of an ictal EEG, usually with a typical frequency evolution, sometimes accelerating after onset and usually slowing before stopping. These characteristics were not seen in our patient. Furthermore, we should clarify that the background between these episodes was not normal, but rather showed a 6–8 Hz, somewhat disorganised posterior rhythm, with intermixed diffuse theta and some low voltage delta. We therefore interpreted the higher amplitude slowing during attacks, as seen in the previously published figure, as an arousal response. We have enclosed with this communication a sample from the same EEG study that shows the typical background activity followed by a definite arousal, corresponding to the notation of “noise”; this arousal is similar to that recorded during attacks (fig 1). In addition, we should have made it clear that, although later alert and responsive both during and between attacks, at the time this EEG was performed, before completing treatment of the shunt infection, he was moderately lethargic between attacks, and became more alert and agitated during them. Space limitations prevented our inclusion of this “baseline” EEG pattern during the initial report.

The fact that the patient responded to autonomic agents rather than to antiepileptic drugs is not a definitive argument against an epileptic origin, as noted by Bernath, although it provides at least circumstantial evidence. Furthermore, it seems unlikely that a diffuse EEG change, as shown in the original figure, would have only autonomic manifestations and would be completely suppressed clinically by labetolol. Simple partial seizures with only autonomic manifestations would be more likely to show a unilateral temporal discharge or an unchanged EEG. For these reasons, we think that our patient in fact had paroxysmal sympathetic storm rather than multiple daily, prolonged autonomic seizures. As noted by Bernath, answering this question definitively would have required intracranial electrode placement, which was not clinically indicated in this case.

Department of Neurology, Brigham and Women’s Hospital, 75 Francis Street, Boston, MA 02115, USA

Correspondence to: Dr E Bromfield ebromfield@partners.org
Horner’s syndrome because Müller’s muscle contracts only about 1.5 mm lid elevation. More than sympathetic dysfunction alone is needed to cause the presented ptosis.

We recently reported a similar case in a 41 year old woman demonstrating involvement of both Müller’s muscle and levator palpebrae superioris clinically and pharmacologically. Orbital imaging showed enlargement of the levator palpebrae/rectus superior complex, which also suggested a local pathology. We proposed a local, possibly inflammatory process of the lid surface anatomy as described by Rice and Gray. A similar explanation might account for the mild aching at the frontal region of the affected side in the patient of Sieb and Hartmann.

More recently a 62 year old man presented to our clinic with a 3 year history of recurrent right complete ptosis lasting 7 to 10 days, occurring once or twice a year with full recovery. The onset of the ptosis was associated with erythema and mild periorbital aching and swelling.

Unfortunately we have not yet been able to find an appropriate treatment. An initial trial with pirydostigmine using the rationale that 15%–20% of patients with myasthenia gravis have negative acetyl choline antibody was disappointing, as was treatment with non-steroidal anti-inflammatory drugs and oral prednisolone. Sieb and Hartmann tried the seroton antagonist pizotifen and prednisolone also without significant improvement.

We do not know the reason for the recurrent complete ptosis in our two patients. Neither can we be sure that the siblings described by Sieb and Hartmann have the same disorder, particularly as in these patients the side of the ptosis alternated. However, we suggest that the syndrome must be due to local disease causing loss of function of the levator palpebrae superioris muscle either alone or in addition to Müller’s muscle.

Management of intracranial bleeding associated with anticoagulation: balancing the risk of further bleeding against thromboembolism from prosthetic heart valves

We read with interest the article by Crawley et al. We respectfully take issue with the authors.

(1) In this article on the management of intracranial bleeding associated with anticoagulation, the authors reported on a patient who had an “isolated paresis of the levator palpebrae superioris and Müller’s muscle” and later developed two new “intracranial haematomas” after heparin therapy. We hope that the authors were referring to either lobar haemorrhage or basal ganglia haemorrhage. If the patient had a subdural haematoma, also classified under intracranial haemorrhage, then a surgical procedure as well as discontinuation of anticoagulation and reversal would have been the preferred treatment.

(2) In their review of the literature, the authors did not discuss the articles by Wijdicks et al and Babikian et al on the relative safety of discontinuation of oral warfarin after intracranial haemorrhage in patients with mechanical heart valves. These authors have found that temporary discontinuation of warfarin for 1 to 2 weeks was relatively safe. (3) Crawley et al estimated a 0.016% daily risk of embolism or 0.67% over 6 weeks. In our experience, although the risk is relatively low, it is in the order of 3% over 30 days.

(4) Crawley et al correctly stated that having reversed anticoagulation in patients with prosthetic heart valves, it is uncertain when to restart it. None of the patients in our experience had recurrence of intracranial haemorrhage on restarting warfarin (after a short period of discontinuation) during their stay in hospital. Thus we do not recommend a prolonged period of warfarin discontinuation in patients who are at high risk of embolism. Additionally we recommend that these patients be screened with echocardiography in evaluating the risk/benefit ratio of warfarin discontinuation and the urgency of restarting anticoagulation.

When replies:

We fully agree with Phan and Wijdicks that if a patient has a subdural haematoma while on treatment with warfarin discontinuation might be required. The particular patient reported had recurrent lobar haemorrhage. Photographs of the brain CT were supplied but not published.

We are aware of the articles by Wijdicks et al and Babikian et al as well as the recently published article by Phan et al, which is an extension of the previous article published by Wijdicks et al. The dilemma of instituting anticoagulation for patients with cardioembolic sources and intracranial haemorrhages is discussed by Hacke in the editorial accompanying the recent paper by Phan et al. Of particular interest is the apparent paradox between the reported embolic risk without anticoagulation with modern artificial heart valves in the range of 4 per 100 patient-years and observed risk in the order of 3% over 30 days in the retrospective studies of Phan et al going up to 20% in the study of Bertram et al.

We agree with Phan and Wijdicks and Wijdicks et al that patients at high risk of embolism should have a limited period of warfarin discontinuation and that each patient needs to be assessed individually as suggested by Hacke. We also agree with Hacke’s suggestion that patients at high risk would be very useful given the difficulties of setting up any form of randomised control trial. The potential prothrombotic effects of haemorrhage and reversal of anticoagulation are also subjects that merit investigation with, for example, thromboembolastography.

A PETZOLD
G T PLANT
National Hospital for Neurology and Neurosurgery, Queen Square, London WC1N 3BG, UK

Correspondence to: Dr A Petzold a.petzold@uol.ac.uk


Sieb and Hartmann reply:

We greatly appreciate the interesting comments of Petzold and Plant who described two sporadic patients showing clinical similarities to our siblings.

Unfortunately, we cannot provide additional evidence for their suggestion that local disease of the Müller’s muscle and the levator palpebrae superioris might cause relapsing, alternating ptosis. Magnetic resonance imaging studies of the orbita as proposed by Petzold and Plant did not show any pathology in one of our patients during an episode of ptosis.

The literature states commonly that oculo-sympathetic parese results only in slight upper eyelid ptosis of 1 to 2 mm. However, our clinical experience in patients with Horner’s syndrome due to carotid artery dissection is different. We still think that an intermittent sympathetic dysfunction is the most likely explanation for the familial disorder observed by us. Hopefully, investigation of additional patients will shed light on the pathology of this unusual disorder.

J P SIEB
Max-Planck-Institute of Psychiatry, Kraepelinstr 2–10, Munich, D-80804, Germany

A HARTMANN
University Hospital Department of Neurology, Sigmund-Freud Strasse 25, Bonn, D-53105, Germany

Correspondence to: Dr J P Sieb sieb@mpspykl.mpg.de


www.jnnp.com
Diagnosis of having mild dementia immediately after the resolution of the delirium. The rate of subsequent dementia in the remaining non-demented patients was three out of 11 (27%) with the initial score on the mini mental status examination 24 or over after the delirium subsided (the incidence rate of dementia was 18.2/100 person-years). In the patients with an MMSE score less than 24 the rate of subsequent dementia after resolution of delirium was 11 out of 26 patients (42%) (the incidence rate of dementia was 25.4/100 person-years). However, in our article we published only the rate of the subsequent dementia in all the patients. The number of patients in the groups based on the MMSE scores was small and the usefulness of the scores in diagnosing dementia was limited in these elderly patients (mean age 82 years). In our study, no corrections were made to the scores of the MMSE text because of vision or hearing impairment or limited education.

BOOK REVIEWS


The authors of this text have sought to provide a handbook in which they present the core clinical knowledge on epilepsy while aiming to be comprehensive and up to date. Chapters cover the usual topics from epidemiology through to surgical treatment and this slim volume certainly packs in a huge amount of information. The reading lists are very useful with statistical information and data from up to date studies. Indeed, a book whose text is made up almost entirely of bullet points proves very difficult to read, and this format does not allow enough space for critical appraisal of the reference studies which the reader will have to be promoted to look up. The authors practical approach to managing epilepsy is useful and I would have liked to have seen more of this. Anticonvulsant drugs are listed with standard accounts of pharmacokinetic and pharmacodynamic data. Most readers would have been interested in a discussion of the relative merits of the newer anticonvulsant drugs and the quality evidence supporting their use in comparison with the older drugs.

This is an excellent little handbook well suited as an introductory reference text for the authors stated target audience of residents in training and general physicians.

Over the past decade the introduction of high dose intravenous immunoglobulin (IV Ig) therapy has improved the treatment of some neuromuscular diseases, particularly multifocal motor neuropathy with conduction block, for which there is no satisfactory alternative therapy. The appearance of this small multiauthor handbook on the use of IV Ig in the treatment of neurological disorders is timely. It has been well edited to produce a clear, easily readable, and relatively even style. The tables are useful and well produced. In general, the authors have stuck to the brief of balancing the relative merits of IV Ig and conventional therapies for their chosen neurological disorder. However, one or two have used the book as the vehicle for general discussion of their chosen disease, accompanied by relatively brief comments on the particular part played by IV Ig therapy.

All regular users of IV Ig therapy must be interested to unravel the mystery of its mode of action. The first chapter of this book considers its possible modulatory effects on a myriad of immunological pathways and mechanisms. Initially we all assumed that IV Ig could only neutralise naturally occurring anti-idiotypic antibodies which neutralise the patient's own pathogenic antibodies. Yet pathogenic antibodies have not been identified as the cause of most inflammatory neuropathies which respond to IV Ig, and after all this time searching one wonders whether they ever will be. It is surprising that nobody has reported whether IV Ig contains natural anti-idiotypic antibodies to the well characterised anticytotoxic T cell receptor antibodies which occur in myasthenia gravis, a disease for which IV Ig seems to be effective according to recent trial evidence. This question of anti-idiotypic activity has been explored more in the Lambert-Eaton myasthenic syndrome without disclosing obvious evidence of their existence against antibodies to the voltage gated calcium channel. As a frequent observer of the almost magical effect of IV Ig on patients with multifocal motor neuropathy, I never fail to be struck by the clear benefit which regularly appears within 48 hours of the first infusion, with improvement in function of muscles which may have been weak for years. Surely this rapidity of the effect of IV Ig in reversing nerve conduction block is telling us something. It seems too quick to be accounted for by some notion of anti-idiotypic neutralisation of pathogenic antibodies, which would be expected to be firmly bound to the target tissue anyway. Possible explanations are raised in chapter 1, although they are not considered specific in relation to this astonishingly prompt clinical effect. IV Ig can modulate T cell control of the production of cytokines, including tumour necrosis factor-α, which may have the potential to cause nerve conduction block.

Inevitably much of this book addresses the principal role of IV Ig in everyday neurological practice: the treatment of idiopathic demyelinating and conduction block polyneuropathies. In this book, motor neuropathy with conduction block and multifocal sensory demyelinating neuropathy are juxtaposed as rather distinct clinical entities; the second being categorised as the Lewis-Sumner syndrome. But the high occurrence of rather non-specific and minor sensory symptoms in patients with multifocal motor neuropathy, and the documentation of sural (sensory) nerve abnormalities in such patients, can we consider these two syndromes as separate, or are they simply peaks within a mountain range? Later on in this chapter considering whether diabetic proximal neuropathy might benefit from IV Ig treatment, given recent evidence of inflammatory infiltrates in cutaneous branches of the femoral nerve, but no clear supporting evidence is presented for this therapeutic notion. The account of the role of IV Ig in standard chronic inflammatory sensorimotor demyelinating polyneuropathy is usefully comprehensive. But despite factually correct and well balanced arguments concerning the relative merits of plasma exchange in IV Ig, this chapter somehow fails to transmit a perspective of when particular clinical circumstances presented by CIDP may merit such therapies, and when to choose each of them. Should plasma exchange be used before IV Ig given that it seems effective in about 80% of such patients compared with 65% for IV Ig? And if plasma exchange is only partially effective, if it has been given first at least it won’t have removed any IV Ig administered as ancillary treatment. In Guillain-Barré syndrome the advice, quite rightly, is to give IV Ig rather than plasma exchange in patients with potential for severe disability. Yet we remain ignorant of the long term benefit of either of these treatments in a disease which is regarded by many undergraduate textbooks as being relatively benign if you survive the bulbar and respiratory failure. It feels as if Guillain-Barré syndrome leaves 16% unable to walk at a year, and up to 5% dead, despite IV Ig or plasma exchange therapy. It would have been good to hear more on the Baltimore view of whether the long term outcome is better after IV Ig than plasma exchange in the acute motor axonal subgroup of Guillain-Barré syndrome. This was an intriguing conclusion of subgroup analysis of the Dutch Guillain-Barré Study Group.

The other disease-specific chapters of the book address less well established, or minority indications for IV Ig. These range from useful discussion on the surprisingly differential benefits accruing to three forms of inflammatory myopathy, to a relatively small trial suggesting partial effectiveness in multiple sclerosis, and largely anecdotal evidence of benefit for Behçet’s syndrome and intractable childhood epilepsy syndromes. Some of these disorders may cause distressingly severe neurological disability. It will be useful to accumulate more data about the possible value of IV Ig in treating them whilst acknowledging that it will be difficult to undertake large formal controlled clinical trials. And no doubt matters will be even more difficult in multiple sclerosis, glaucoma and any future trials of IV Ig may have to be in the form of add on therapy to other better established yet only partially effective treatments for the disease, such as β-interferon.

The final section of this book will be of great help to neurologists. It concerns the rather dry subject of preparation of IV Ig, and its safety and tolerability. As any regular IV Ig user knows, these questions crop up regularly. The clear and succinct accounts provided by this book is welcome. For instance, tabulation of the characteristics of the 18 commercially available IV Ig products compares factors such as the suggested dosage used in each of these may be related to some of the side effects.

A review of the different methods for inactivating known infectious agents which may be present in the parent plasma pool reminds us that, whereas each method is highly effective, none of the current processes can guarantee total inactivation of viral particles. There is practical advice about assessing whether it works in an individual patient, whether it works usefully in overcoming disability, and how patients and their families can be trained for domiciliary administration of IV Ig.

A useful little book to keep in your office if you use IV Ig regularly to treat neurological diseases. But it leaves untouched some of the most fascinating questions posed by IV Ig. Why does it produce its effect so quickly? Why is it so effective in a supposed autoimmune disease, multifocal motor neuropathy, which is worsened by prednisolone therapy? Surely the answer will illuminate the pathogenesis of diseases such as multifocal motor neuropathy.

Michael Donaghy


The authors state that this book is aimed at the primary care physician or perhaps the “general” neurologist who is not an expert in the movement disorders field. As such, they have emphasised the clinical aspects of each condition including differential diagnosis with only an outline of the various treatment options. It is divided into five sections. The first covers basic principles taking us back to the basic phenomenology of movement disorders and also basic neuroanatomy. There then follows an appropriately complex chapter on motor speech disorders with Parkinson’s as the main example in such a volume. Section two covers all aspects of idiopathic Parkinson’s disease. As is common with multi-author texts there is a great deal of repetition between chapters on the epidemiology, aetiology, pathophysiology, and clinical features of the condition. The chapters on neuroprotection and symptomatic therapy for the condition are more balanced and divided into sections specifically aimed at the less experienced clinician. However, they only cover North American practice where tolcapone remains available, whereas madopar, apomorphine and cabergoline are not. Apart from associated problems such as sleep disorders, autonomic dysfunction, psychiatric problems, and surgery for Parkinson’s disease are shorter and thus more suitable for the busy general practitioner. The last three sections cover Parkinson’s plus syndromes including progressive supranuclear palsy and multiple system atrophy. These chapters are more balanced but still sparsely detailed. This is probably inevitable in a book of this size...
point. Section four covers hyperkinetic movement disorders with separate paragraphs on tremor disorders, essential tremor, dystonia, hemifacial spasm, Huntington's disease, and tardive dyskinesias. The detailed explanations of myoclonus and the stiff person syndrome are inappropriate in such text. The final miscellaneous section comprises Wilson's disease, gait disturbance, and post-traumatic and psychogenic movement disorders. Much of this is also too specialised.

As a text for the general practitioner to either read or use as a reference source, this book is far too long. This stems from the repetition in the earlier sections and the excess detail throughout. This, combined with the strongly North American orientation of the book, particularly in terms of epidemiology and medication, means it will be of little value to the European primary care physician.

C E CLARKE

Localization of brain lesions and developmental functions. Edited by D RIVA and A BENTON. (Pp 165, £39.00.) Published by John Libbey, Eastleigh, 2000. ISBN 0 86196 5999X

The richness of this subject has become apparent with the development of tests assessing an increasing array of aspects of cognitive function. This, coupled with intelligent use of structural and to an increasing extent functional, brain imaging, encourages the development of developmental brain behaviour modules as never before.

We are fortunate to have a book which reviews progress in the area—even if only to show the gaps in our understanding and the vast amount of work remaining to be done. The chronology of localisation provides an interesting historical perspective in an introductory chapter.

There follows one of four chapters by his coeditor Daria Riva, the first on memory and temporo-sensory structures. The clinical literature is usefully presented; general conclusions are offered as fact rather than as the hypothesises they are—although none the less interesting for that—namely, that the cerebral cortex encodes information which is then codified in parahippocampal structures. The function of the hippocampus is to analyse the components of experience and to construct relations between different aspects of experience in flexible and potentially infinite ways, thereby creating a uniquely personal mental map.

Then follow three essays on lateralisation of hemisphere function as derived from studies of callosal deficits—congenital and acquired. The picture which tends to emerge from this format is non-peer reviewed. The final miscellaneous section comprises Wilson's disease, gait disturbance, and post-traumatic and psychogenic movement disorders. Much of this is also too specialised.

As a text for the general practitioner to either read or use as a reference source, this book is far too long. This stems from the repetition in the earlier sections and the excess detail throughout. This, combined with the strongly North American orientation of the book, particularly in terms of epidemiology and medication, means it will be of little value to the European primary care physician.

R O ROBINSON


This is the third edition of a book which stems from an original series of 12 articles on Neurological Emergencies, published by this Journal in 1993. In this current edition there are 13 chapters; the “new addition” is the short final chapter by Dr O'Brien on criteria for diagnosing brain stem death. The titles of the other chapters have remained the same as they were in 1993 and cover a broad range of neurological, psychiatric, and neurosurgical emergencies. The chapters on cardiac arrest have possibly become remarkably little; but why change a winning team? The contributors are leading authorities in their respective topics.

Each chapter has been updated where necessary and all are well written. Very short summary boxes are particularly useful. This combination of strengths is appropriate, as the text is clearly not intended to be exhaustive. In the acute situation, the tables of differential diagnoses (the chapters on status epilepticus and obstructive respiratory paralysis deserves special mention in this regard), boxes devoted to management (I continue to find the section on management of tonic-clonic seizures particularly very helpful), and the flow charts (notably the prediction of outcome of coma—invaluable for the intensive care consultation) are quickly located and will be extremely useful. The text adds “meat to these bones”, but if more detailed information is required this could always be found from the references, hopefully after the crisis has passed.

From the title of the book, it will be purchased by predominantly neurologists. Thus, the chapters on traumatic brain injury and raised intracranial pressure may be less often read than the others. This is a pity, as these issues are well covered and have been extensively revised and updated.

There are always going to be minor quibbles with omissions and the relative weighting of topics from a multiauthor book such as this. I could not, for instance, find any reference to the diagnosis and management of neuroleptic malignant syndrome. It could be argued perhaps that more space could have been devoted to HIV infection and its management than the three pages allocated, compared with twice this space on brain abscesses.

The book is compact and paperback, but will require a bag or briefcase for visits to the intensive care unit and accident and emergency department, as it is still too large to be accommodated by most white coat pockets. A strong case could also be made for keeping a copy on the neurology (and neurosurgery) ward rather than in the library. Specialist registrars may well wish to invest in their own copy. In the next few years, due to a combination of changing junior doctors' hours and the finite duration of training imposed by our current training system, it might also be wise for the consultant to keep a copy on their bedside cabinet.

DAVID J BURN

Dementia is a big subject and this is a big book. The first edition was edited by John O'Brien and Alistair Burns and for this edition Professor Levy's retirement has catalysed John O'Brien and David Ames into sharing the editor's role. It is a role that seems to have been fulfilled excellently. Since the last edition the dementia field has not so much moved as leapt forward and this text valiantly does its best to keep up. To a certain extent this is an impossible task. It is simply not possible to keep abreast of the rapid developments in the fields of molecular genetics and biology. It could be argued that to do so is pointless as those who want and need to know of the latest developments will access journal or web based information. Indeed, to my mind at least, should provide a repository for all those esoteric bits of knowledge, the general reviews allowing access to an area not one's own and the basic principles underlying a subject. This multiauthored text does all of those and it is those chapters that try to set out the general principles that succeed the best. Reading the chapters on topics as diverse as semantic dementia and spectroscopy was a much welcomed and (needed) educative exercise. There were many others. Not surprisingly however, the usual caveats to a text book are there. Attention or diligence. The first two sections provide an expert review does on page 275: "A bulletin on April 15, 2022 by guest. Protected by copyright. http://jnnp.bmj.com/ J Neurol Neurosurg Psychiatry: first published as 10.1136/jnnp.70.6.812 on 1 June 2001. Downloaded from www.jnnp.com
young patients with stroke, inherited cerebral vascular disorders, and vascular dementia. However, as the text stands, it is highly recommended to those who practice cerebrovascular medicine.

IAN BONE


In just 149 pages and nine separately authored chapters, Professor De Leon has produced a practical guide to the clinical, radiological, and pathological features of Alzheimer’s disease, principally aimed at junior hospital doctors, nurses, and other paramedical workers, as well as general practitioners, with an interest in the disorder. The book is beautifully illustrated, and the many diagrams are helpful and informative. Reisberg relates the changes in daily life that affect patients with Alzheimer’s disease, from the very beginnings of change through to the very end of life. The accompanying drawings are delightful and bring home the misery of the illness in a very real way. The utility of functional imaging in persons at risk of Alzheimer’s disease is discussed and lavishly illustrated by Jagust. A detailed anatomy of the hippocampus and associated structures by De Leon follows, chronicling the early involvement of these regions and emphasising the value of research in differentiating persons with mild cognitive impairment, as well as frank dementia, from cognitively intact people. However, here, the reader is left with the (unavoidable) impression that MRI can act as a sensitive diagnostic for Alzheimer’s disease, neglecting that equivalent degrees of hippocampal atrophy can occur in patients with other forms of dementia—for example, frontotemporal. Braak eloquently covers the topographic origins and spread of the pathological changes. Iqbal reviews the structure of the neurofibrillary tangle and its affects on neuron function. The role of glial cells in the formation and removal of amyloid is discussed by Wegiel and its chemical properties by Wisniewski. Poirier reviews genetic factors, although the book suffers somewhat here from the advances made in this area since the publication in 1998. For example, the number of causative mutations in the presenilin-1 gene listed has now nearly trebled and the identity of the presenilin proteins, their function, and relation to amyloid formation are much better understood. None the less, overall, this is an excellent book that will have great appeal. I would recommend a look, even its purchase, particularly as the authors’ royalties are being donated towards the establishment of a young researcher fund.

DAVID M A MANN


Just over 20 years ago, the notion that nerve cells transplanted to a damaged adult brain could not only survive but also make functional connections would generally have been regarded as heretical. Since that time, however, the field of embryonic neural transplantation has grown almost exponentially and has emerged as a credible discipline. Aside from considerations of functional repair to brain damaged hosts, the technique has also been revolutionary as a tool for investigating neural development and specific aspects of neurodegeneration. This Neurotransplant volume is the 36th in an ongoing series and has an internationally acclaimed neuroscientist as first editor. In particular, Professor Stephen Dunnett was instrumental in establishing embryonic neural transplantation as an experimental technique from its earliest days in the late 1970s and has remained its leading scientific figure in the United Kingdom. The volume itself is clearly devised as a handbook for aspiring neural transplantors, with those wishing to hone their techniques. Rather than serving merely as a manual, however, it also provides a timely historical review and exhaustive reference source for this young science. It is divided into three sections which, respectively, focus on the numerous possibilities for obtaining neural cells for transplantation, the techniques of implanting the neural tissue, and, lastly, tips for enhancing neuronal survival and function in the host.

The first of these aspects is perhaps the most controversial, especially with respect to potential clinical applications for neural transplantation in Parkinson’s and Huntington’s diseases. It has been abundantly clear from the earliest use of this technique in human patients that obtaining embryonic tissue would provide extreme practical problems and cause the most ethical concern. It is extremely useful, therefore, to find up to date chapters on stem cells, immortalised cell lines, and engineered cells as sources for transplant material. Similarly, the chapter on intracerebral gene transfer using various viral vectors provides an alternative approach to studying development and even repair, representing a potentially exciting tool for the future.

The section on transplant methods serves as a useful review of a technique for introducing transplant material to the host. It also includes a chapter on glial transplants as an experimental method for the remyelination of central nervous tissue. In general, this section draws on the consensus of experience from the leading laboratories in the field, and underlines the expertise required to undertake successful grafting using techniques which, to the uninitiated, may seem deceptively simple. In addition, one entire chapter is devoted to the technique of intrascolar grafting which, as in vivo model, has several advantages. In particular, the accessibility and ease of visualising graft growth in this model allows many of the basic scientific questions on neural transplantation to be addressed.

The final section on the factors governing graft survival and function is, by necessity, perhaps the most speculative. The reason why over 90% of transplanted neurons fail to survive remains largely obscure and is almost certainly multifactorial, reflecting host and graft factors. The potential role of apoptosis is discussed in some detail as are the various methods by which the infant tissue process by specific means such as captase inhibition or the use of trophic factors. The chapter by Brundin explores the nature and timing of transplant cell death and includes discussion of antioxidants and general strategies to prevent cell death. One potential utility of combining several neuroprotective approaches is pertinently addressed. Several other chapters in this section centre on the difficult issue of acceptance of rejection of transplant tissue by the host. The likely need for genetically engineered transplant tissue for successful grafting across species is discussed despite the relatively low immunogenicity of embryonic neural tissue and the (semi) privileged transplant sites within the blood-brain barrier. These issues are particularly pertinent to the perception of embryonic porcine neural tissue in human neurodegenerative disease.

In conclusion, this book provides an exhaustive summary of the neurobiological theory and techniques, both established and potential, relating to neural transplantation. It is clearly a highly specialised area now emerging from its infancy and is unlikely to have general appeal to clinical neurologists. Certainly for those intending to use this immensely powerful technique in the context of basic neuroscientific research, the book will be invaluable. Similarly, for those with an interest in the potential application of neural (or glial) grafting in human disease, the volume will provide an excellent rationale for the technique and give a state of the art account of where we stand. The illustrations are generally of extremely high quality and the layout is excellent to 1999. If the volume is read sequentially there is a degree of repetition among the numerous authors but this would be my only quibble. If the field of neural transplantation “takes off” in the decades to come as I think, this volume is likely to find itself a classic, heralding the definitive arrival of this novel and innovative technique.

PAUL READING


My first impression on being asked to review this book was “who needs another text book on dementia?” This opinion quickly changed as I browsed through the 11 chapters and often alighted on actions that caught my attention. After several bournings I found that I had actually read substantial chunks of virtually every chapter.

The greatest virtues of the book are the choice of topics, which encompass almost all of the rapidly evolving and controversial areas in dementia research including the genetics of Alzheimer’s disease, chromosome 17 and frontaltemporal dementia; dementia with Lewy bodies; mild cognitive impairment; the status of subcortical vascular dementia; neuropsychiatric manifestations of Alzheimer’s disease; and therapy with cholinesterase inhibitors, hormones, and anti-inflammatory drugs. Secondly, the fact that all of the chapters are written by acknowledged experts in the field. Thirdly that the coverage is international (with contributions from the United States of America, Canada, the United Kingdom, Germany, France, Finland, and Italy); and most notably, the short delay between writing and publication is evidenced by the inclusion of many references from 1998 and some from 1999.

The book provides, therefore, excellent summaries of recent advances in each of the topics covered, all of which are covered in an accessible style. For those interested in a particular area (which is these days inevitably limited in scope) it is valuable to have such a collection of fully referenced reviews from the broad range of other topics. It is clearly no less informative, who are likely

This is a small book with a formidable task. The editors describe it as written for “busy clinicians, especially general practitioners”. The layout of the book is certainly clear and the writing mostly jargon-free as intended. Chapters are arranged roughly in accordance with the divisions of chapter F40-48 of ICD-10: “Neuropathic stress-related and somatoform disorders”. These initial chapters cover the symptoms, diagnosis, epidemiology, comorbidity, and aetiology of each of the five main disorder groups. A useful if perhaps somewhat confusing chapter deals with the important subject of comorbid depression and anxiety. The final chapter, which will almost certainly be the most heavily thumbed, deals with treatment. The book includes many clear diagrams and tables and the final treatment chapter includes some easy to follow treatment algorithms.

There is no doubting the psychopharmacological emphasis and expertise of this book, as would be expected from the editors. Psychopharmacological and treatments appear as appetisers to virtuoso descriptions of the latest theories and applications of drug treatments. In the section on psychological treatments it is stated that “unfortunately, many of the psychological techniques used require specialised training, and access to practitioners with these skills is often difficult”. This is arguably the case, but in practice psychological interventions probably still come somewhat higher up the treatment algorithm than 6 to 12 months of high potency benzodiazepines. The rationale for this seems to be rather confused by the contradictory ond treatments it is stated that “unfortunately, there is a lack of evidence for the efficacy of psychological treatments compared with the results of pharmacological treatment.”

Preceding that is a section on epilepsy syndromes, including a discussion on epilepsy classification and epidemiology and the place for EEG and neuroimaging—the “diagnosis” part of the title. Introducing these sections are chapters on anticonvulsant mechanisms, consequences of seizures, and genetic influences.

The preface suggests that the book is intended as a practical guide and reference for clinicians and investigators. The contributors are generally the names to be expected in the different fields, drawn largely from north America (none from Europe). Does it succeed? Not as well as it might.

As a practical guide it does not deal with the investigation of many epilepsy situations, such as the encephalopathic epilepsies of infancy—no with rational drug strategies in partial and generalised epilepsies.

It is curiously lacking in many management issues such as subclinical seizures, “subclinical” or transient cognitive impairment, or the implications of the abnormal EEG in autism—a particularly hot topic at the moment. It is silent on the question of life expectancy of patients with a history of sudden unexpected death—issues which the clinician will be asked about. The management of status epilepticus is well described, but there is nothing about outcome—a question uppermost in parents’ minds. The section on quality of life is theoretical and research oriented. How to approach constraints in lifestyle and what may be done to ameliorate them is void.

The section on adolescents’ needs, transitional clinics, and organisation of epilepsy clinics in general would have been welcome. Vagal nerve stimulation, mentioned as a major new development in the preface, gets about two and a half column inches in the section on Lennox-Gastaut syndrome.

The book shows signs of lack of editorial grip. Section on Landau Klein syndrome or pyknolepsy are found in several places, all saying more or less the same thing. Although I suspect a subsidiary aim was to link basic and clinical sciences, there is no cross referencing between them (or between any other chapters for that matter).

A major text in this section deserves to do well, but I am afraid that in this instance the discriminating buyer will look elsewhere.


The most useful part of this book is an account of each of the anticonvulsant drugs. Concisely summarised is the evidence for efficacy, or lack of it, of each. Included is a section on epilepsy surgery.

It is approached by a section on general principles, which is a miscellany including (oddly) status epilepticus but also treatment decisions, anticonvulsant profiles, dosage considerations, pharmacokinetics and some treatment decisions. These two sections comprise the “therapy” of the title.


There is a constant debate as to the value of textbook in general in this information technology age. This is perhaps most marked in the field of molecular genetics, which is moving at such a pace that a chapter could almost be drafted or updated on a monthly basis given the rapidity of new developments. Nevertheless there is value in collating all the current information and attempting to put a field in context. I think that such is the intention of a volume such as this. Kelloggkether has amassed an impressive field of contributors to this large volume on ataxic disorders. The book spans some basic neuroanatomy and neurophysiology of the cerebellum through clinical approaches to ataxic patients and then several chapters describing the many disorders that can affect the cerebellum and its connections, thus producing ataxia. Perhaps unfortunately the area of progress in this field most of the chapters are given over to the genetic forms of ataxia and a relatively few to the non-hereditary ataxias. This of course does not represent the true pattern seen in a general or even specialist neurology clinic. However, I see no way around this as our knowledge of the non-hereditary is rather scant at present.

This of course is in marked contrast with the progress over the past 5-10 years in understanding of the genetic ataxias where we have seen identification of numerous forms of dominant and recessive ataxias. In most of the major areas the genes are identified and we have now moved into the field of specific tumour types. All chapters provide authoritative and valuable reviews and conclusions drawn are based on a thorough assessment of the literature. There are, of course, some overlaps between individual chapters with a common theme—for example, molecular pathogenesis—but this is inevitable and allows each contributor to stand alone. This notwithstanding, the editors have achieved overall cohesion of presentation so that this book can be viewed as a simply a collection of reviews. It is inevitable that the time required to complete such a large project means that some important recent developments, such as the discovery of the natural ligand for the growth hormone receptor, could not have been included in the excellent chapter on hypothalamic-pituitary physiology and regulation. Any criticism of this book would be minor but I was disappointed that an otherwise very thorough chapter on neuroophthalmological evaluation did not deal with the more practical aspects of clinical assessment including choice of methods for field assessment. Overall, the editors have carried out their stated aim of providing information in a single book which is of value to the various specialists who treat patients with pituitary mass lesions and function as members of a multi-disciplinary team. I would recommend it to clinical endocrinologists, to neurosurgeons seeking an in depth knowledge of the endocrinological aspects of pituitary mass lesions, and to neuroendocrine pathologists who will appreciate the breadth of coverage and the extent to which discussion of pathogenesis, pathology, and clinical management have been skilfully combined.

JOHN MONSON
molecular biology to try and illuminate the pathogenic pathway. These experiments are brought up in the relevant chapters.

A constant problem in a multiauthor book such as this is a non-uniformity of style or perhaps even worse, repetition from one chapter to the next. I am pleased to note that this has largely been avoided and apart from a rather brief general introduction to most of the chapters which could apply to some others each author does not labour the point on the dominant ataxias, for example. However, sufficient information is given in each chapter to allow the reader to delve into that chapter alone to understand SCA 1 or SCA 3 for example. I think this is testimony to both good authorship and good direction from the editor. However, there are one or two minor irritations. For example, the referencing system in chapter 1 is different from other chapters. Also, within this chapter there is a small error but it makes part of the chapter difficult to read. The abbreviation for long term depression and long term potentiation are given as the same and therefore that section is more difficult to understand than it might be. These are small quibbles. My only other disagreement with the book came in chapter 27 when the author describes most late onset cerebellar degeneration as being different from other 


This book offers a description of the neurological syndromes that may occur after cardiac surgery, including both central and peripheral complications. This is followed by information on neuropsychological outcome, quality of life, imaging, and neuropsychology. The information supplied is reasonably comprehensive. The data on prognosis are a little thin, but there is probably enough here to advise patients, and the relatives of patients who have sustained damage from a cardiac embolus, for whom it would be useful, although it would be available from other sources. The one complication that I did not see mentioned was hypertensive encephalopathy, which I have seen in a teenage patient with apparently “normal” blood pressure after cardiac transplantation, but who for many years preoperatively had a systolic blood pressure of about 70.

The next section of the book deals with markers of cerebral injury and patient monitoring techniques including both EEG and cardiac emboli; it subsequently moves on to management techniques. These two parts of the book would be of very limited interest to neurologists, and would be of greatest interest to anaesthetists. The information is fairly comprehensive although it deals with prevention, part of the subtitle of the book, implicitly rather than explicitly and similarly identification of high risk patients is covered very sparsely indeed.

Neurologists will be familiar from other environments with the vast majority of the neurological syndromes that may occur after cardiac surgery, for whom it would be a useful introduction to the neurological consequences of cardiac surgery.

JOHN BOWLER

Neurosurgical classics II. Edited by ROBERT H WILKINS and GLORIA K WILKINS. (pp 592, US$95.00). Published by American Association of Neurological Surgeons, Rolling Meadows, 2000. ISBN 1 897284 74 X.

The first volume of this book, which was published in 1965 under the auspices of the Harvey Cushing Society, now The American Association of Neurological Surgeons, republished 52 papers of outstanding interest in the history of neurosurgery which had been published before 1940. Those papers which had been originally printed in languages other than English were translated into the English language. Because of demand the first volume was reprinted in 1992.

This second volume of neurosurgical classics reprints a further 58 papers published since 1940. These papers are divided into 31 groups each of which is preceded by an introduction outlining relevant background material and references. Rather curiously, the references for the papers are given in the contents section but are not attached to each individual paper.

A wide range of topics is covered. Thus, in the first section on diagnostic techniques we have the first papers on CT published by Hounsfield and Ambrose in 1973 and the subsequent pioneering papers on MRI published over the next few years. Other topics covered include papers on intracranial pressure, topical haemostatic agents, microneurosurgery, skull base surgery, and the first descriptions of anterior operations for cervical disc disease. The original illustrations are used although in some cases eye covers have been added to the photographs to protect the identity of the patients. This is perhaps a little superfluous as most of the patients concerned have probably been dead for many years as a result of the time that has elapsed since publication and the conditions for which surgery had been carried out. Some of the papers have been shortened and a handful of papers are included from the pre-1940 era going back as far as 1910—for example, Halstead’s report of two cases of pituitary tumour operated on by the transphenoidal route.

This book makes fascinating reading. It is hard to believe that there is a neurosurgeon who will not want to possess a copy or having obtained it, will not want to reread some of the articles. It is perhaps a pity that the first volume was not republished as a companion to the present one so that it would have been possible for those of us who do not possess the first volume to purchase both at once. Many, perhaps most, of the papers it contains are of such abiding interest that they are still often quoted in lists of references. To add to its desirability it is beautifully produced and printed and sufficiently well bound to make it a robust bedside book.

R S MAURICE-WILLIAMS