Hashimoto’s encephalopathy responding to plasmapheresis

A 47 year old man presented to the emergency department of our hospital. He was born in Uruguay, but had lived in Australia for many years and had not travelled overseas recently. He had no relevant medical history or record of illicit drug use. He had a 2 week history of a coarse, postural tremor of the upper limbs and an unsteady gait and was brought to hospital after an un witnessed fall at home. On arrival he was alert but “irritable”; shortly thereafter he had a generalised seizure, which was treated with intravenous diazepam and phenytoin. Several hours later he had failed to regain consciousness: he was breathing spontaneously, was afebrile, and had no neck responses, was afebrile, and had no neck stiffness. He was commenced, followed by oral prednisolone.

Several hours later he had failed to regain consciousness and was intubated for airway management and had a normal precontrast and postcontrast cerebral CT. A lumbar puncture disclosed normal CSF pressure (15 cm H2O), with a high protein (1.34 g/l) but normal cell count and glucose. Angiography of the vertebrobasilar system was normal. Intraoperative heparin was started, and later intravenous acyclovir. After extubation, he had ongoing cognitive impairment and remained generally hypoflexic with extensor plantar responses. His admission was characterised by a fluctuating, but slowly improving, delirium. He had short term memory deficits, visual and auditory hallucinations, and paranoid delusions. His upper limb tremor persisted and he had a second generalised seizure. His EEG was diffusely slow without epileptiform activity; this later improved. C-reactive protein was 58 mg/l but other investigations were normal or negative, including routine haematology and biochemistry, erythrocyte sedimentation rate, ANA, ANCA, HIV, and syphilis serology. Anti-cardiolipin antibodies were negative. His thyroid function was normal and he was a non responder to radioactive iodine uptake. His estimated glomerular filtration rate was 58 ml/min but other investigations were normal.

The volume of plasma exchanged per treatment was 1.5 times twice the total plasma volume, and the number of exchanges was consistent with the treatment of other autoimmune neurological disorders.

His condition improved after the first plasma exchange, and by the end of treatment he was able to dress and feed himself and converse in English; he was able to return to part time work as a cleaner. This clinical improvement was accompanied by a further decline in antibody concentrations (figure, point B). He remained well, with slowly rising antibody titres and another seizure occurred plasmapheresis (three exchanges, total 21.0 litres) again resulted in a decline in antibody concentrations (figure, point C) and clinical improvement. He continued taking prednisolone and azathioprine throughout this time. He remained euthyroid and had no goitre.

The patient later had a further relapse, associated with generalised seizures. A trial of intravenous gammaglobulin was without effect and his condition again improved promptly with plasmapheresis. When last seen in the outpatient clinic he was clinically well, had no new cognitive symptoms, and was taking prednisolone, azathioprine, sodium valproate, topiramate, and warfarin. He was building a barbecue at home and his wife thought he was as well as he had ever been. Two days later he was found dead at home by his wife. Initial postmortem examination failed to find a definite cause of death and further pathological investigations are proceeding.

After the initial report by Brain et al in 1966, there have been several other individual case reports and series of patients with neurological syndromes associated with high titres of antithyroid antibodies. Our patient followed the typical course described in other cases of Hashimoto’s encephalopathy, with tremor and seizures, fluctuating encephalopathy, high CSF protein, and a diffusely abnormal EEG. The abnormalities in brain MRI have been described, others have had normal MRI, as did our patient. The unique feature of the present case was the patient’s clinical and serological improvement with plasmapheresis. A treatment that has not been previously described in connection with this condition. The pathogenesis of Hashimoto’s encephalopathy remains unclear. Several theories have been proposed, including a generalised abnormality of the immune system, cerebral vasculitis, recurrent demyelination, or a toxic effect of thyrotropin releasing hormone on the CNS. It is clear, however, that an abnorimity of thyroid function itself cannot explain this condition, as many patients described in the literature are euthyroid either at the time of presentation or relapse. An autoimmune basis is suggested by the high concentrations of antithyroid antibodies and improvement with immunosuppressive therapy. The precise role of antithyroid antibodies in Hashimoto’s encephalopathy is a surrogate marker for other, as yet unknown, antibodies that cross the blood-brain barrier and initiate an autoimmune encephalopathy. Various immunosuppressive treatments have been used in this condition, including corticosteroids, azathioprine, cyclophosphamide, and intravenous immunoglobulin.

This patient’s clinical course demonstrates that the response to corticosteroids may be incomplete and that additional clinical and serological improvement can be achieved with the use of plasmapheresis. It is unclear whether the patient’s death was related to his underlying neurological condition. If it was, then it is a further indication of the unpredictable course and outcome of Hashimoto’s encephalopathy.

We thank Dr R Lindeman for his assistance with plasmapheresis.

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Meningoencephalitis after streptokinase treatment

The mechanisms underlying allergic reactions to streptokinase treatment can be divided into three major groups: immediate IgE mediated (type I), immune complex deposition (type II), and an IgG mediated (type II). Apart from cerebral haemorrhage the only previously reported neurological complication of streptokinase therapy is the Guillain-Barré syndrome. We present a case of meningencephalitis after streptokinase therapy.

A 52 year old man presented with classic features of an acute anterior myocardial infarction. Treatment with oral aspirin and intravenous streptokinase was initiated. Fir-
teen minutes later he developed a diffuse erythematous skin rash, pyrexia of 39°C, a tender throat, and became hypotensive. The streptokinase infusion was discontinued and intravenous hydrocortisone and chlorpheniramine were administered. His symptoms settled within 24 hours. He made an uncomplicated recovery and was discharged after 5 days. Two days later he returned with a painful, swollen throat and a similar rash, which again responded to hydrocortisone and chlorpheniramine treatment. Four days later, 11 days in total after the streptokinase, he developed general malaise, an occipital headache of gradual onset, double vision, vomiting, and word finding difficulty. There was a bilateral photophobia, neck stiffness, or skin rash, but he had a pyrexia of 40°C, an abbreviated mental test score of 7 out of 10 (he failed to recall the date, current year, and prime minister), bilateral sixth nerve palsy, an indistinct left optic disc, mild dysarthria, and an expressive dysphasia. His patient is unique in that he had all three of the reported “allergic” reactions after streptokinase therapy: immediate, serum sickness-like, and autoimmune. In future, meningococalphelitis occurs as a complication of streptokinase therapy should be borne in mind.  

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Atypical course of neuropsychiatric Gaucher’s disease: follow up from early infancy until adulthood  

Gaucher’s disease is caused by a deficiency in glucocerebrosidase which gives rise to the accumulation of glucosylceramide (glucocerebrosides) in the lysosomes of cells mainly found in the reticuloendothelial system. Type 1, the chronic adult form, is the most frequent, and characterised by splenomegaly, hepatomegaly, pancytopenia, and skeletal degeneration, but does not involve neurological manifestations. Type 2, also called acute neuropsychiatric, is an early infantile form, usually terminating life in 1 or 2 years. Type 3 is a chronic form which affects the nervous system, usually in late childhood or adolescence. We report here the case of a patient with Gaucher’s disease who was diagnosed in early infancy (6 months) in a paediatric insti-
The treatment was started at the age of 27 by the cerebroside β glucosidase of placental origin alglucerase (Ceredase, Genzyme, Cambridge, MA, USA), with 60 Units/kg body weight, by intravenous perfusion every 2 weeks until the age of 31. After this period, alglucerase was replaced by the recombinant enzyme imiglucerase (Cerezyme, Genzyme, Cambridge, MA, USA) and the patient has been treated up to the present (age 34) with the same posology and an identical time interval. Thus the patient has been treated for 8 years so far.

The propositus was heterozygous for the L444P and the D409H mutations. Sequencing showed that the patient did not have other point mutations. His father carried the L444P mutation and his mother the D409H mutation (figure). Informed consent was obtained for genetic studies.

The treatment was well tolerated. No antibodies against either form of the enzyme were found. The asthenia rapidly disappeared. His spleen, still hypertrophied at the age of 28, was found to be normal (7.5 cm for the great axis) at the age of 31. The aggravation of the gait stopped. The ophthalmoplegia remained unchanged. The paroxysmic dystonic manifestations disappeared. The tremor of the head and of the arms had also decreased in intensity. During this period, the only new medications were the substitutive enzymatic therapy and carbazamazepine (600 mg/day). We are aware of the fact that the prescription of carbamazepine may in itself ameliorate paroxysmic dystonic manifestations. No clonic attacks occurred. FA Hommes, ed. Taubert W, Friesel S, von Hungen M, Ochsner C, ed. Dystonic syndromes in diagnostic human biochemical genetics. A laboratory manual. New York: Wiley-Liss, 1991:387–417.

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The number of mutations involved in Gaucher’s disease is great.1,2 The L444P mutation is often associated with a more severe neurological manifestation. Patients carrying the L444P mutation and the D409H mutation have been reported to develop a form of type 3 Gaucher’s disease in which the oculomotor signs are predominant and the visceral symptoms are discrete. This case differed significantly from these other cases.

In conclusion, the patient had a neurological form of Gaucher’s disease and could be evaluated over 3 decades. Before enzyme substitutive therapy, the patient and his family reported a progressive deterioration of his neurological state. When he was treated, visceral and haematological symptomatology became normal; and there was a stabilisation or even a slight improvement of his neurological symptoms as well as modification of mood and behaviour, allowing a better integration in social life. Thus some patients with Gaucher’s disease with early neuropsychological manifestation may have a benign course and profit considerably from enzyme supplantation.

We acknowledge Mrs Marri Verhoek for her skilful contribution. The follow up was performed in collaboration with the French Evaluation Committee for Treatment of Gaucher disease (CEFG), who also we gratefully acknowledge. This work was possible through grant PHRC AOA 94033 from Assistance-publique-Hôpitaux de Paris, and grants from the lysosomal disease association VML and the Caisse Nationale de Prévoyance CNP.

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Creutzfeldt-Jakob disease in a young person with valine homozygosity at codon 129: sporadic or variant?

To date there have been 52 reported cases of variant Creutzfeldt-Jakob disease (vCJD) in the United Kingdom. All cases that have undergone genetic investigation have been methionine homozygotes at codon 129 in the prion protein (PrP) gene. There has been speculation as to whether valine homozygosity or heterozygosity at codon 129 confers resistance to vCJD, delays clinical onset of disease, or may lead to a clinical syndrome distinct from cases of CJD described so far. Here we report on a young patient with CJD who was a valine homozygote at codon 129.

A previously well 27 year old electrical engineer complained that he had difficulty concentrating at work. His wife noticed that he had become more forgetful and increasingly agitated which she attributed to stress at work. He was seen in December 1997 and at this stage appeared anxious and with communicative difficulties in that he could understand what his wife was saying to him but could not understand anyone else. Neurological examination was otherwise unremarkable. Haematology and biochemistry, a cranial CT, and an EEG were normal. He was diagnosed as having an anxiety state and referred to a psychiatrist who thought that an...
organic brain syndrome was more likely. By February 1998 it was clear that he had a receptive and expressive dysphasia and right extensor plantar response. Thyroid function, B12 and folate, an autoimmune screen, protein electrophoresis, serum copper, serum ceruloplasmin, heavy metal screen, pharynx screen, IgA antibodies to gliadin, serological tests for Trophegnum and human immunodeficiency virus tests were all normal. Protein in CSF was mildly raised at 0.62 g/l and correlates with BBB permeability. Glycophorin, transferrin, and CSF 14–3–3 protein were negative. Repeat EEG demonstrated a left hemispheric slow wave focus, cranial MRI showed atrophy of the whole of the left hemisphere, and a SPECT perfusion scan demonstrated marked underperfusion of the posterior temporal lobes, and parietal lobes bilaterally. MRI of the sella and appendix was negative. Western blot analysis of frozen cerebral tissue showed a positive reaction in a single patient. This was thought to be due to a presenile dementia with concomitant Alzheimer’s disease. All other studies negative, including amyloid plaques were identified. Immunocytochemistry showed a spongiform encephalopathy which was most marked in the basal ganglia, with widespread neuronal loss and gliosis. No amyloid plaques were identified. Immunocytochemistry for PrP on lymphoid tissue in the cerebral cortex and the cerebellum, and no PrP plaques were present. Immunocytochemistry for PrP on lymphoid tissue in the spleen and appendix was negative. Western blot analysis of frozen cerebral tissue showed a PrP\textsuperscript{res} type 1 pattern.1 Early age of onset, protracted psychiatric prodrome, and duration of illness distinguish sporadic Creutzfeldt-Jakob disease from sporadic motor neuron disease. The presentation of those cases is described. Firstly, the case represents sporadic CJD, of which there have been only two cases younger than 30 in the United Kingdom since 1970.2 Neuropathological review of these cases has found changes in the brain consistent with sporadic CJD; full clinical and genetic data are not available on these cases, but neither showed evidence of PrP\textsuperscript{res} accumulation in lymphoid tissues. The lack of characteristic neuropathological features of CJD in the brain, the absence of detectable PrP in the tonsil appendix and spleen, together with a PrP\textsuperscript{res} type 1 pattern in the cerebral cortex all provide supportive evidence for this being a case of CJD, similar to the other rare cases occurring in valine homozygotes with a type 1 PrP\textsuperscript{res}.3 A less likely explanation is that this case may represent bovine spongiform encephalopathy (BSE) infection in a valine homozygous person without the characteristic pattern of PrP glycosylation occurring in BSE and related disorders in animals and humans.4 This case emphasises the importance of detailed clinical, neuropathological, genetic, and biochemical studies in all cases of suspected CJD, particularly in young people with a valine homozygous or heterozygous codon 129 PrP genotype. Further investigation of such cases by strain typing studies would be required to establish their relation to the BSE agent.

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4 The National Creutzfeldt-Jakob Disease Surveillance Unit and Genotypes Dataset. Taken from table 4.5 published in Marriage, divorce and adoption statistics (series FM2). Office for National Statistics.

Multiple sclerosis treatment trial precipitates divorce

We have noted an unusually high rate of divorce among participants in a recent small treatment trial of multiple sclerosis.5 Of the 29 patients in the study, 19 were married at entry. During the 18 months of follow up, six patients (31%) became involved in divorce proceedings. In four of these, the unaffected spouse left the marriage for another partner. There was a transient breakdown in one other marriage, which did not lead to divorce, after an extramarital affair by the unaffected partner. Since the study ended, there has been one further divorce after an extramarital affair by the unaffected partner. Those patients who became divorced were not distinguishable by their disability, the efficacy of their treatment, or the duration of their disease or marriage. The divorce rate in this study, equivalent to an annual rate of 21% of married couples, is considerably greater than the annual divorce rate in the United Kingdom for age and sex matched married couples of 2.4%-3.1%.6 Thus physical disability due to any cause is a risk factor for divorce7 and multiple sclerosis is no exception.8 However, this effect is not sufficient explanation to account for the exceptionally high divorce rate seen during this study. In one patient in our study, the most severely disabled patients with multiple sclerosis were four times more likely to have divorced than the less disabled; but even among the most disabled the prevalence of divorce was 3.5%-15% of all prevalent patients.9 We suggest that participation in a treatment trial indirectly precipitates divorce, by exposing marital dissatisfaction in the unaffected spouse. The possible explanation may be that trial participation focuses attention on the affected spouse’s disability. Alternatively, perhaps the frequent attentions of an interested medical team during a trial relieve the unaffected partner of a sense of responsibility towards his or her spouse. Another interpretation might be that recruitment to therapeutic trials is biased towards those patients who perceive a greater degree of dissatisfaction with their personal situation. To the best of our knowledge, in no previous treatment trial in multiple sclerosis, nor indeed of any other disease, has such a high rate of divorce been noted.

In the light of these findings it may be prudent to make patients and their spouses (or partners) aware, during the recruitment interviews for clinical trials of the strains which participation may expose in their relationship.

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Allodynia: a sensory analogue of motor neuron reflexes in a hyperaesthetic patient reporting instantaneous discomfort to another’s perceived sudden minor injury?

Parietal injury may affect spatial cognition in at least three ways: right sided damage may cause left inattention (unilateral neglect), whereby the patient ignores or fails to attend to objects or events on the contralateral left side of extrapersonal space1; in a rare extension of this disorder, the patient may also experience the presence (often fluctuating) of an addition to their space, an ‘phantom limb’—for example, a further arm at the midline in addition to a normal one on the right, and a paralysed, neglected, or “missing” on the left. Finally, in the Gerstmann syndrome there may be, after left parietal damage, simultaneity, left-right disorientation, acalculia, agraphia, and problems with finger (or other body part) localisation or identification. Conversely, with amputation or loss (even congenital) of a limb to an otherwise healthy individual, a phantom limb may be experienced,1 with the vivid hallucinatory experience of the continued presence of that limb, parietal mechanisms have again been involved.

The parietal cortex interconnects with the ventral premotor cortex which, as area E5 in monkeys, contains neurons that discharge both when an animal grasps or manipulates objects, and when it sees another individual making similar actions.2 These “mirror neurons” seem to represent a system that matches observed events to similar, internally generated actions, and thus forms a link, as the author’s note, between observer and actor.
In humans, areas in the left inferior frontal and right superior parietal cortex become active both when producing and when seeing finger movements in others. Could similar mirror activity arise in a purely sensory context, such that a person, due to inhibitory failure, may experience pain in a finger or limb when seeing sudden trauma (for example, a blow) to a corresponding area in another person? We report the anecdotal account, from a widow, of her late husband's apparent experience of such "mirror pain" or, as we would suggest, "allodynia".

The deceased, a long time smoker, died in late February 1993 with the diagnosis of "extensive metastatic carcinomatosis", antecedent cause "carcinoma of the right lung". (The widow, however, questions the lung cancer diagnosis, and claims that symptoms of serious rheumatoid disease involving cervical spine and dysphagia were misinterpreted.) As a consequence of increasing pain and stiffness beginning in the neck and upper body, and chest symptoms, he underwent radiography of the cervical spine and chest in August 1990, disclosing opacities in the right lung and miliary shadow deviations; he had increasing difficulty swallowing with food inhalation. Unwillingly, he underwent radiotherapy in early November 1990 to alleviate dysphagia, although according to the widow subsequent gastroscopy indicated that this may have been unnecessary.

He was reported to be very sensitive to touch; even the slightest hand contact gave the impression of sharp fingernails. Of particular interest was his widow's recent observation that "If I slightly knocked my finger, spontaneously showing him, he would immediately grasp his own finger and say "do n't do that" (meaning not to show him). He actually felt it. If I merely commented (that I had knocked my finger), there was no such reaction". In interview, she recounted other similar events. The experience was suddenly immediate and intense, and, apparently, qualitatively similar to the hypersensitivity typically described by early recognition of pain in others. Perhaps during infancy avoidance of noxious stimuli is facilitated by early recognition of pain in others. Although mirror motor neurons may be fundamentally important in learning to act, an adaptive role is far less obvious for perceiving another's pain. Perhaps during infancy avoidance of noxious stimuli is facilitated by early recognition of pain in others. Alternatively the phenomenon may merely be adventitious consequence of disruption of convergent sensory systems. Thus hyperalgesia, where a light touch induces an unpleasant sensation in the same person, is typically attributed to dysfunction of convergent sensorimotor neurons in the neuraxis, though any of several CNS levels may be involved. However where, as here, a separate person is implicated, there may be additional limbic involvement, given the rather intensely emotional aversive aspects of the sensory experience. Unfortunately no CT or MRI seem to have been performed of the brain, but it is probable that there was fairly widespread CNS involvement. He had also, apparently, experienced hearing trauma in the ear. It would be of interest to know whether similar "allodynia" has been seen after known damage that includes left inferior cortex (cuneal region), or the rostralmost portion of the right superior parietal lobule. It would also be interesting to get persons, normal or hyperalgesic, to note reactions to noxious stimuli in others while judging the intensity of mildly aversive tactil stimuli they receive themselves.

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Acquired hepatocerebral degeneration: full recovery after liver transplantation

Liver diseases may give rise to variable degrees of neurological impairment, which mostly consist of the syndrome of hepatic encephalopathy, due to the toxic effect of ammonia on the brain during episodes of liver decompensation. In a minority of patients, repeated episodes of liver failure can lead to a chronic progressive encephalopathy, not necessarily related to hyperammonaemia, known as acquired hepatoencephalopathy or hepatic encephalopathy (AHD). The pathogenesis of AHD is unclear, but the relation with the acute form of hepatic encephalopathy seems a crucial point. Cerebral deposition of manganese may have a pathogenic role. The disease may appear after one or more episodes of hepatic coma or, rarely, become manifest in the absence of them. Neuropathology typically discloses degenerative changes in the basal ganglia. The modern techniques of neuroimaging disclose these lesions in vivo. The clinical picture may result from neuroanatomical changes and movement disorders usually being prominent. The syndrome is poorly responsive to medical therapy, thus being considered largely irreversible.

We report a patient with AHD who was cured by liver transplantation.

A 59 year old man came to us in November 1997 for a neurological consultation before inclusion in the waiting list for liver transplantation. He had a history of chronic hepatic disease—alcohol and HCV related liver cirrhosis—which had begun some years before. No familial hepatic or neurological diseases were reported. In 1995 he had an episode of hepatic encephalopathy, consisting in somnolence and confusion lasting 36 hours. At the time of examination, the patient had stopped alcohol consumption 1 year before; liver failure was grade C-10 of the Child-Pugh classification. Copper balance was normal. Neurological examination and EEG gave normal results. The patient was put on the waiting list for liver transplantation. In February and March 1998, he had two episodes of mild ascites with signs of encephalopathy (confusion and asterixis), both reversed by medical therapy. In April 1998 the patient began to complain of sleep disorders, tremor, dysarthria, motor slowness, and subtle cognitive dysfunction, not reversed by medical therapy for hepatic dysfunction. On 6 June 1998, his neurological suitability for liver transplantation was reconsidered. He seemed alert, oriented, and cooperative, with a slight slowness of psycho-motor activity. The neurological examination showed hypomimia, dysarthria, bradykinesia, oral dyskinesia, and mild bilateral hand tremor. Neuropsychological examination showed a remarkable impairment of information processing control (attention, visu-
lance, psychomotor speed, intelligence) with sparing of memory (table). An EEG disclosed diffuse slow activity. Cerebral MRI showed circumscribed bilateral lacunae on the lentiform nuclei on T1 weighted images. On 10 July liver transplantation was performed, with a successful outcome and a rapid improvement of the neurological disturbances. Immunosuppressive treatment with cyclosporine did not induce neurological complications. One month after liver transplantation only a mild dysarthria persisted. An EEG was normal. A neuropsychological assessment 3 months after surgery showed a remarkable improvement in the cognitive performances, especially in information processing control tasks (table), whereas cerebral MRI was unchanged. Twelve months later, neurological examination was normal and cerebral MRI disclosed a reduction of basal ganglia lucencies. Neuropsychological testing documented a slight further improvement in control functions of information processing, with a slight decline in some memory performances (table). No other neurological problems emerged during subsequent early follow-up.

This patient had an AHD presenting with movement and cognitive disorders. The first consisted in disabling movement disorders, with severe bradykinesia and dystonia. The second impairment included both decreased functioning of the frontal executive functions and single function deficits (especially visuospatial abilities and language), conveying a picture of “hepatic dementia”. Cerebral MRI documented the basal ganglia lesions usually seen in AHD.1 Both the clinical and the neuroradiological abnormalities were reversed by liver transplantation. After surgery, the recovery from neurological impairment was prompt and complete, whereas neuroimaging improvement occurred later. This outcome resembles that previously seen in a patient with Wilson’s disease.2 Despite the different pathogenesis, the similarities between AHD and Wilson’s disease are remarkable for pathological lesions and clinical and neuroradiological presentation.1,3 Liver transplantation has been reported to reverse neurological manifestations in most patients with Wilson’s disease.2,3 Liver transplantation in AHD is confined to two cases. A cirrhotic patient with improved chronic cognitive and motor disorders after liver transplantation was described in 1990.4 Twenty years later, Powell et al reported a case of successful liver transplantation in AHD. Their patient had a significant improvement in intellectual functions and chronic neurological signs after surgery. Our present finding confirms these positive results and also documents that neuroradiological abnormalities are reversible. It is conceivable that both Wilson’s disease and AHD are characterized by an early stage neurodegenerative process mainly affecting the basal ganglia, where MRI detectable hepato-cerebral degeneration is slowly reversible and liver transplantation can rapidly improve neurological symptoms. The duration of the disease does not seem to be a crucial factor, as patients with long standing encephalopathy may also recover after liver transplantation both in AHD4 and in Wilson’s disease.1 This conclusion has pathogenetic and therapeutic implications: the presence of signs and symptoms of chronic hepato-cerebral degeneration, both in Wilson’s disease and in the acquired non-Wilsonian form, should not be considered a contraindication for liver transplanation and surgery may be the elective treatment for the neurological syndrome.

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CORRESPONDENCE

Unexpected sudden death after lateral medullary infarction

I read with interest the study of Fitzek et al1 which included 15 patients with lower brain stem infarction. One patient with a “complete Wallenberg’s syndrome” (No 15) died during the period of observation. Details on that patient’s death are not included in the paper.

Through personal communication with the authors I have learned that this patient’s death No 15, a 69 year old man, died unexpectedly 14 days after an acute brain stem infarction. Because the family refused a necropsy, we do not know with certainty whether some other acute process was involved in the patient’s death. However, an ECG and chest radiograph after presentation had been normal.

Recent reports2–5 have described patients who experienced unexpected sudden cardiac-respiratory arrest seven days after lateral medullary infarction, at a time when they were convalescing well and were stable medically and neurologically after a stroke which caused minimal motor disability. The reports have speculated about mechanisms by which cardiorespiratory arrest occurred; cardiac arrhythmia is among these.6,7 Although I do not know many pertinent details surrounding the death of the 69 year old man described by Fitzek et al, I speculate that his death may have resulted from cardiovascular arrest caused by an intermediate event in which the lateral medullary infarction and surrounding brain tissue disturbance (possibly ischaemic penumbra) influenced brain stem cardiac and respiratory centres together with autonomic pathways in a manner which at this time is not understood.

A recent neuropathological study8 of five patients disclosed similar characteristic ischaemic lesions in the solitary tract nuclei of the medulla after subacute hypoperfusion of the brain during acute heart failure. It was speculated that these medullary lesions had in turn caused autonomic instability which precipitated death in each case. It is plausible that ischaemic lesions of the solitary tract nuclei result initially with some lateral medullary infarctions, and that such lesions may in turn precipitate some occurrences of cardiorespiratory arrest.

Postictal psychosis related regional cerebral hypoperfusion

I wish to comment on the postictal psychosis related regional cerebral hypoperfusion reported by Fong et al.9 Based on their findings of hypoperfusion on SPECT within the time frame of postictal psychosis, the authors argue against the hypothesis that postictal psychosis is a psychogenic mimic of Todd’s phenomenon. Two previous studies have shown a focal increase in cerebral blood flow on brain imaging during traditional motor Todd’s paresis.10,11 An angiogram during Todd’s paresis may demonstrate “blush” perhaps representing loss of cerebrovascular autoregulation at the site of the epileptic focus.12 Hence, hypoperfusion may signal hypofunction, and the findings of Fong et al are indeed consistent with postictal psychosis as a Todd’s equivalent.

The strongest argument that postictal psychosis is not a Todd’s equivalent is the delayed onset of psychosis compared with the decerebrocorticocaudal syndrome of Todd’s motor, cognit, and visual phenomena.13,14

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One of the most interesting fields of research in epilepsy in the past 5 years or so has concerned cortical dysgeneses. In some series of chronic epilepsy, overt dysgenesis underlies 15% of all epilepsies, and more subtle forms might account for some apparently cryptogenic cases. This book is therefore timely. It is a record of the proceedings of a conference held in Venice in October 1997, within the framework of the Mariani Foundation Colloquia in Childhood Epilepsy. The book is organised into sections on cortical development, animal models, electroclinical imaging and neuropathological studies, genetics, and surgical treatment. The faculty and chapter authors are distinguished figures in this research field largely from the United States, Canada, and Italy.

The recognition of the importance of these conditions in epilepsy has been due to the introduction of structural MRI and also the advances in understanding of the processes of cortical development. The second field particularly is one in which advances are being made rapidly, both clinically and in the laboratory, and the authors and editors do a superb job in marshalling this information into a readable and well organised form. I found many of the chapters exceptionally interesting. The heavy emphasis on molecular genetics and pathology is appropriate in this area and is a model for how the modern topics of epilepsy should be approached.

My only reservation about the book is that in this fast moving field some of the basic science and genetic data are already out of date.
but otherwise the information is of high standard. The clinical chapters are exemplary, however, and I particularly enjoyed the two fascinating chapters on surgery for epilepsy in cases with dysgenesis. A minor grumble about the book is not about the content, but the poor standard of book production (a common trend in medical books), with for instance horrible margins and without a list of contributors. In all other ways, though, this is a superb book, and one which I thoroughly and wholeheartedly recommend to both clinical and basic scientists. It is a definitive contribution to this important area.

SIMON SHORVON


There is something about the autonomic nervous system that causes undergraduate students and doctors alike to lose interest, switch off and for their eyes to glaze over. Professor Alison Brady suggests in her preface that this is due to “uninspired teaching and inadequate coverage in many textbooks”. Although one can only imagine that Professor Brady is an exception to the first generalisation, this book, an obvious labour of love, is a brave attempt to correct the second.

The text is best suited to the physiology undergraduate student, medical or otherwise. Certain chapters will also appeal to the specialist registrar starting out in areas such as cardiology, respiration, gastroenterology and, of course, neurology. It is concisely written in a style that is willing the student to stay with her, to follow her logic and read on and beautifully illustrated with clear diagrams and cartoons as well as many good quality electron micrographs. Although Bradin herself is based in Oxford, much of Gaskell and Langley’s pioneering study of the autonomic nervous system was in Cambridge around 100 years ago. This book therefore begins with a historical overview to set what follows in historical perspective. Then follow chapters on anatomy, neuromuscular, and synaptic transmission, the mechanisms involved and their function, and finally, the relevant body systems. This is not a clinical textbook but mention is made of possible pharmacological manipulation of the autonomic nervous system where appropriate.

If you have always wanted to get to grips with the autonomic nervous system but have found the available literature too dry or anti- quated, now’s your chance!

GILLIAN HALL


This book, by its own admission, is neither a comprehensive textbook nor teaching manual. The author’s stated intention is for it “to be a bedside reference to which to quickly look up how to perform a technique … or to look up reference values…”. It is just that—a reference book or paper data base of up to date normal values. In the case of commonly collected data, this is tabulated with respect to age, sex, height (F waves), and body mass index. In all cases, the number of subjects, machine settings, and skin temperature are documented.

Ideally all EMG departments would collect and compile their own normal values but in reality this seldom happens. Given this is failing, this is the book for the purest who, for example, wishes to check that his lateral ante-brachial cutaneous sensory peak latency falls within two standard deviations of the mean. Or whether that slight apparent prolongation of median F waves is acceptable in the young, six foot something basket ball player. As such, it is a useful reference book to be found on the shelf of your EMG laboratory, if not actually always with you by the bedside.

Its wider appeal for the novice or junior practising electrophysiologist is its descriptions and diagrams detailing electrode positioning and examples of typical, expected waveforms. It is for this reason that I might find myself with this book at the bedside, especially for some of those more obscure cutaneous sensory nerves.

Buschbacher intends his book to be a practical manual with lists of acceptable differences, helpful hints, references, and pointers to additional reading and alternative techniques as well as space for the operator to make his or her own observations.

GILLIAN HALL


This is a clear, basic textbook outlining the main neuropsychiatric syndromes prevalent in patients with multiple sclerosis. It can be divided into three main sections. (1) An introductory chapter summarising briefly the pathogenesis, pathology, and clinical features of multiple sclerosis and concentrating on some useful definitions and guidelines for diagnosis, (2) four chapters on the psychiatry of multiple sclerosis—namely, depression, bipolar affective disorder, pathological laughing, and crying and psychosis, and (3) five chapters on cognitive changes in multiple sclerosis, specifically examining their nature, detection, course, and neuroimaging correlates. The emphasis of the book is somewhat predominantly on the cognitive dysfunction associated with multiple sclerosis. This is a well presented section with a clear and comprehensive review of research in this area. By contrast, it is somewhat disappointing that the section on psychiatry of multiple sclerosis is so small, particularly as depression in multiple sclerosis is, according to the author, more prevalent than cognitive dysfunction.

Again, this psychiatry section is clear. The authors deplore this development and the objective demonstrated and measured. The authors deplore this development and the main purpose and thrust of this volume is to rectify it. They, a psychiatrist and a neurologist, together run a memory “complaints” clinic and this is fitting as it is the diverging pattern taken by these two clinical disciplines as much as the emergence of cognitive neuropsychology that is responsible for the fragmentation of the clinical concept of memory disorder.

The contributions are from psychologists, psychiatrists, and neurologists; some are clinicians, some researchers; some are clinical, some theorectical. Buschbacher intends his book to be a practical manual with lists of acceptable differences, helpful hints, references, and pointers to additional reading and alternative techniques as well as space for the operator to make his or her own observations.

GILLIAN HALL


Until the end of the 19th century little distinction was made between complaints of poor memory due to disorders that have since been shown to be organic in nature and memory disturbances of less certain provenance—for example, Ganser’s syndrome. Since then, and increasingly over the past decade, memory disorder as a clinical concept has narrowed to embrace only those disorders in which memory impairment can be objectively demonstrated and measured. The authors deplore this development and the main purpose and thrust of this volume is to rectify it. They, a psychiatrist and a neurologist, together run a memory “complaints” clinic and this is fitting as it is the diverging pattern taken by these two clinical disciplines as much as the emergence of cognitive neuropsychology that is responsible for the fragmentation of the clinical concept of memory disorder.

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GILLIAN HALL

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The choice of topic is sometimes surprising: flashbulb and flashback memories may be of interest in their own right, but they are unlikely to figure prominently in most memory clinics and sit rather awkwardly here. There is little on the effect of normal aging or on alcohol related memory disorders. The writing is at times uneven and in too many chapters detailed accounts of historical development take precedence over contemporary analysis. There are nevertheless useful contributions on the neuropsychological investigation of malinger- ing and a refreshingly pragmatic chapter on recovered and forced memories.

This is a book which, although something of a curate's egg, approaches memory as a clinical subject with a breadth and comprehensiveness unlikely to be found elsewhere. It is to be strongly recommended, not least for those already engaged or planning to set up memory clinics and to psychiatrists with a desire to learn more about higher mental function.

BRIAN TOONE


Whether it is because peripheral nerve has a limited repertoire of responses to pathological insults or whether it is because advances in other areas of neuropathology have side-lined interest, for many years peripheral nerve disease has been the Cinderella of that specialty. Indeed there have been very few monographs on this subject since Boy Weller first published his Pathology of Peripheral Nerve in 1977. Now, with an increase in knowledge of peripheral nerve disease, and advances in electron microscopy and the genetics of inherited neuropathies, the publication of this Atlas of Peripheral Nerve Pathology is timely.

Broadly the book is divided into two sections. In the first the author takes us through the normal light and ultrastructural anatomy of peripheral nerve. There then follow chapters on biopsy techniques and importantly a section devoted to artefact. After chapters on morphometry and abnor- mal structure of peripheral nerve the reader is led into the second section which is devoted to pathological changes. In summary, there are sections on the pathology of the axon, myelin sheath, Schwann cell, intesitium, and vaina nervorum. This is a handsome well illustrated book with good quality and well annotated photomicrographs, many in colour. The electron micrographs are clear and crisp. The text is well written and indexed. This book is primarily an atlas so it would be unfair to criticise deficiencies in the text. However a discussion on the indications for nerve biopsy with some suggested guidelines would have been useful. I think some mention should have been made of the procedure's potential complications.

This book has obvious appeal to clinicians with an interest in disease of the peripheral nervous system and to neuropathologists, but the generalist in both specialties will find it useful. For such a heavily illustrated book it is reasonably priced at £125.

DAVID J DICK


Schmidley's book on CNS angiitis is an absolute gem. He concisely summarises the salient information about this rare and often puzzling condition that affects the blood vessels of the brain. The writing is clear and lively and easy to read and digest. After summarising the data, Schmidley always lets the reader know where he stands on issues. He reviews the major common features of each condition and yet also mentions unusual and rare features and often illustrates with excerpts from individual patients.

The book begins with a rather in depth but concise review of the clinical and pathological features and the diagnosis and treatment of isolated CNS angiitis. Included is an excellent chapter on pathogenesis which reviews complex immunological theories in a very readable summary form. Later chapters deal with postpartum angiitis, cases of supposed angiitis diagnosed by angiography, and various infectious and systemic and vascular disorders that have been posited or proved to include angiitis of the brain's vasculature. Coverage of individual disorders such as neurosarco-coidosis, Behcet's disease, scleroderma, Eales' disease, etc includes concise but data rich summaries. The entire book covers 165 pages of text. The illustrations are excellent and there are many useful tables that contain summaries of the data. The reference list is extensive.

Schmidley emphasises several very important points that are not widely known to neurologists. I mention only a few here. (1) Isolated CNS angiitis may represent a stroke. (2) The angiographic findings that radiologists dub as vasculitis are quite non-specific and are found in various non-angiitic conditions. (3) Angiograms are often normal in patients proven to have isolated CNS angiitis because the vessels (arteries and veins) involved are usually quite small and the brain imaging findings in this condition are very non-specific. Isolated CNS angiitis can only be confidently diagnosed by biopsy. (4) Stroke is almost never the first presentation of polyarteritis nodosa or temporal arteritis. (5) Most strokes in patients with lupus erythematous are not attributable to a CNS vasculitis. (6) The brain lesions in Behcet's syndrome are probably related to a meningoencephalitis rather than a true angiitis.

I recommend this little book highly to all neurologists. It will prove very handy when confronted with difficult patients of undiagnosed brain diseases and will be useful when looking up the key findings and literature refer- ences in patients suspected of having any form of systemic or CNS vasculitis.

LOUIS R CAPLAN


In the past decade, many new treatments for migrainous headache have been developed and marketed. The flow has slowed up in the past year or two, not least because several good theoretical ideas have not proved valuable in clinical practice, and the comprehen-sive review of current drugs is therefore timely. Professor Christopher Diener, who has published distinguished research on the pathophysiology of headache as well as its treatment, has assembled a panel of authori- ties to review all current treatments for migraine, both analgesic and prophylactic. At the end of the book there are individual chapters on cluster headache, tension head- ache, paroxysmal hemicranias, drug induced headache, and post-traumatic headache.

In the main section on migraine, all the triptans are covered, including almotriptan and frovotriptan, which have yet to reach the market, as well as opioids and the different drugs used in prophylaxis, including flunarizine, valproate, and gabapen- tin. The industry based pharmacologist who developed each drug gives an account of its theoretical properties, and then one of the principal clinicians responsible for the trials reviews its role in clinical practice. Each chapter is thoroughly referenced, and the book will prove to be an excellent source of references to classic trials. There is some duplication within the pairs of chapters, and occasionally commercial pride seems to inhibit a truly independent discussion of the merits of the drugs. Much of the clinical material, inevitably, amounts to a catalogue of trials that does not lend itself to easy con- sequent reading. Some of the more experimen- tal clinicians make valuable comments—notably Goadsby emphasising the 2 and not the 4 hour response data for naratriptan, Fer- rari on the analysis of recurrence rates for different drugs, and Tfelt-Hansen and Saxena on the limited likely role of 5HT, receptor inhibition on the mechanism of suc- cessful prophylaxis. Jim Lance distils a lifetime's experience of prophylaxis into six pages. The reviews of simple analge- sics in tension headache by Schoenen, and of post-traumatic headache by Keidel are excel- lent, providing material difficult to find elsewhere.

In many respects this is an outstanding book. It provides an invaluable source of published evidence for the treatment of patients with headache. It needs some dedication to read it through, but it would be a useful addition to every departmental library.

R C PEATFIELD


This multiauthor book aims to provide physi- cians with an approach to the management of patients with chronic neurologic disease.

The first part of the book describes a gen- eral approach to the management of neurologically disabling conditions. The three chapters entitled Nature of the problem, Char- acter of the solution and Measurement of effectiveness. The first describes the preva- lence of disability with particular reference to the United States and then goes on to describe the nature of the disease, impairment, disability, and handicap, with an inter- esting discussion of the meaning of illness. The second chapter provides a good overview of a particular approach to rehabilitation. It describes a specific framework that encom- passes many of the ideas and concepts that are common to rehabilitation throughout the world. The final chapter considers issues sur- rounding measurement of outcome.
The second part of the book applies this approach to specific diagnostic groups. The book has been well edited with each of the chapters following the same standard format with the nature of the problems being covered with sections reviewing the epidemiology of the disorder, the nature of the disease, and the associated impairments, disabilities and handicaps followed by sections on the character of the solution discussing management techniques and outcome measurement. A particularly good chapter is on spinal cord injury by Pamela Ballard with very specific descriptions of the impairments, disabilities, handicaps, and quality of life issues associated with spinal cord injury and their management. Other chapters are less coherent which may reflect the fact that for some disorders (spinal injury, multiple sclerosis) rehabilitation approaches are better established than for others. Each of the chapters illustrates the approach using clinical anecdotes. These emphasise the importance of the physician taking a patient centred approach. Overall this book is worth reading for its description of a rehabilitation approach. The second section is less likely to appeal to neurologists but may have wider appeal to non-neurologically trained physicians working with patients with chronic neurological disease.

DIANE PLAYFORD


The field of autism research has been growing very fast in the past decade. The book reflects the increasing need to understand the complexity of medical findings on the biological basis of the autistic syndromes. The authors provide the readers with a useful framework in which much emphasis is placed on autism as a disease with many causes and a wide range of clinical presentation. A great deal more is known than at the time of writing of the second edition (1992), and this new edition reflects the update at all levels. It is a comprehensive reference book as well as stimulating reading for various disciplines as such as electrophysiology, neuropathology, and brain imaging; currently available studies are summarised and discussed pinpointing limitations and suggesting new relevant questions. The chapter on genetics has been extensively rewritten, and even the lay reader will find useful information about the development of understanding genetic components of autism. Practising clinicians working with patients affected by the syndrome will find of particular interest the chapters outlining the clinical picture of autism developing from infancy to adulthood, in addition to those discussing the relation of autism with medical diseases and the phenomenon of comorbidity. Different diagnostic criteria for Asperger syndrome are discussed, and clear guidelines are given for early screening of infants.

I cannot imagine anyone being disappointed by reading this book and, in particular, cognitive psychologists will be flattered by the claim that “the most interesting constructs of the whole field of autism have been generated by cognitive psychologists”.

FULVIA CASTELLI

Table 2 Treatment and prophylaxis of cryptococcosis and toxoplasmosis in HIV infection

<table>
<thead>
<tr>
<th>First choice</th>
<th>Alternative</th>
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<tbody>
<tr>
<td><strong>Cryptococcosis:</strong></td>
<td></td>
</tr>
<tr>
<td>Acute infection</td>
<td>Amphotericine B, 0.7 mg/kg/day iv and flucytosine, 100 mg/kg/day orally or iv in 4 divided doses for 2 weeks, then fluconazole, 400 mg orally/day for 8 weeks Fluconazole 200 mg orally/day</td>
</tr>
<tr>
<td>Suppressive therapy</td>
<td>Fluconazole, 400 mg orally/day for 10 weeks, or Fluconazole 200–400 mg orally/day for 10 weeks and flucytosine 150 mg/kg/day orally or iv in 4 divided doses for 2 weeks Amphotericine B, 0.6–1.0 mg/kg iv/week, or Itraconazole, 200 mg orally/day</td>
</tr>
<tr>
<td><strong>Toxoplasmosis:</strong></td>
<td></td>
</tr>
<tr>
<td>Acute infection</td>
<td>Pyrimethamine 100–200 mg loading dose (2 days), then 50–100 mg orally/day plus folic acid 10 mg orally/day+ sulfadiazine 4–8 g orally/day for at least 6 weeks Pyrimethamine 25–75 mg orally/day plus folic acid 10 mg orally/day+sulfadiazine 500–1000 mg orally/6 h</td>
</tr>
<tr>
<td>Suppressive therapy</td>
<td>Pyrimethamine plus folic acid plus clindamycin 900–1200 mg iv/6h or 300–450 mg orally/6h for at least 6 weeks, or Trimethoprim 160 mg plus sulfamethoxazole 800 mg/8h orally or iv for at least 6 weeks Pyrimethamine plus folic acid plus clindamycin 300–450 mg orally/6h, or Trimethoprim, 160 mg plus sulfamethoxazole, 800 mg orally/day Dapsone 50 mg/day plus pyrimethamine 50 mg/week plus folic acid 25 mg/week</td>
</tr>
<tr>
<td>Prophylaxis (patients with positive IgG serology and CD4 count &lt;100/mm³)</td>
<td>Trimethoprim 160 mg plus sulfamethoxazole 800 mg orally/day</td>
</tr>
</tbody>
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