Lack of association of nephrilysin polymorphism with Alzheimer’s disease and Alzheimer’s disease-type neuropathological changes

Sporadic Alzheimer’s disease is a polygenic disease and the relation between many genetic risk factors and the development of Alzheimer’s disease has been controversial. Accumulation of amyloid β-protein (Aβ) in the brain is the neuropathological hallmark and thought to be a key event in the upstream stage of pathological cascade of the disease. Although increased production of Aβ is expected to be one of the pathogenesis of familial Alzheimer’s disease due to mutations in presenilin 1, 2, and amyloid β-protein precursor genes, there is no evidence of up regulated synthesis of Aβ in the brains of patients with sporadic Alzheimer’s disease. In addition, aging is the most major risk factor for the disease. These findings suggest the possibility that reduction of the catabolic system of Aβ due to aging causes the formation of senile plaques in sporadic disease. Therefore, proteolytic enzymes of Aβ might be related to the development of sporadic Alzheimer’s disease.

One of the enzymes responsible for the degradation of Aβ is nephrilysin (NEP). This is a membrane bound metalloendoproteinase which is ubiquitously expressed in many tissues including the CNS. It cleaves Aβ 1–42 between amino acids 9 and 10 and between amino acids 37 and 38. Reduced mRNA and protein concentrations of NEP in the brain from patients with Alzheimer’s disease were reported, suggesting that low concentrations of NEP contributed to the accumulation of Aβ. Recent investigation showed that NEP inhibitor infusion into the brain resulted in increased deposition of Aβ, indicating that NEP regulates the proteolytic catabolism of Aβ in vivo. There is a dinucleotide repeat polymorphism in the 5’ region of the NEP gene. A lower molecular weight allele of NEP gene polymorphism is associated with low amplitude of P300 and increased risk of psychiatric illness in Alzheimer’s disease. Therefore, decreased NEP correlated with the densities of the senile plaques, dystrophic neurites, and neurofibrillary tangles in the hippocampus and superior temporal gyrus in patients with Alzheimer’s disease and non-demented subjects were examined by χ² test. The same analysis was performed in the subgroups divided by ApoE ε4 status. The correlations between NEP gene polymorphism and the densities of the senile plaques, dystrophic neurites, and neurofibrillary tangles in the hippocampus and superior temporal gyrus in the brains from patients with Alzheimer’s disease and non-demented patients, and ages at onset and durations of illness in Alzheimer’s disease were examined by Kruskal-Wallis test. We used five sets of data, NEP genotype, NEP allele, longer allele, shorter allele, and the sum of GT repeats of two alleles as NEP gene polymorphism to classify our samples. Statistical significance was defined as two tailed probabilities of <0.01. All analyses were performed using the computer software StatView J-4.5 (Abacus Concepts).

The genotypic and allelic frequencies of the NEP gene in Alzheimer’s disease and non-demented patients are shown in table 1. Five types of alleles, which represent 19–23 GT repeats and nine genotypes, were found in our samples. There were no significant differences in the frequency of NEP genotypes between Alzheimer’s disease and non-demented in the total patients (table 1). ApoE ε4 carriers and non-ApoE ε4 carriers (data not shown) showed no significant differences in the densities of the senile plaques, dystrophic neurites, and neurofibrillary tangles in the hippocampus and superior temporal gyrus in the total cases, and ages at onset and durations of illness in Alzheimer’s disease. There was no correlation between NEP genotype and ages at onset or durations of illness. The results remained non-significant when we performed similar analysis using the other types of NEP polymorphism such as longer allele, shorter allele, and the number of sum of GT repeats of two alleles to classify our samples. The genotype, longer allele, shorter allele, or the number of sum of GT repeats of two alleles were not associated with the genotype or allele of ApoE ε4 data (data not shown). The ApoE ε4 allele was significantly associated with Alzheimer’s disease (p=0.0001).

To our knowledge, this is the first study to examine the genetic relation between a catalytic enzyme of Aβ and sporadic Alzheimer’s disease. Although the present study does not demonstrate association of NEP with the development of Alzheimer’s disease, the lack of association suggests that NEP may not play a significant role in the pathogenesis of sporadic Alzheimer’s disease.
Human T lymphotropic virus type I (HTLV-1) associated myelopathy acquired through a liver transplant

Subacute myelopathy (HAM/TSP) is the main neurological manifestation of human T lymphotropic virus type I (HTLV-1) infection. This virus is found in Central Africa, Caribbean countries, and Japan. It is transmitted through sexual contacts, during lactation, and by blood transfusions. The risk of seroconversion after blood transfusion is 40%–60%. Around 5% of titic carriers will develop clinical manifestations; only 0.3% of them will have a myelopathy. Immunosuppression enhances the risk of infection, reduces the latency, and accelerates the clinical pictures. We are reporting the first documented case of HTLV-1 infection through an organ transplantation in a western country.

In another organ recipient the vehicle of the virus was the blood transfused during the surgical procedure.

A 44 year old woman developed alcoholic cirrhosis and hepatocarcinoma. On 5 October 1998, she received a liver transplant followed by cyclosporin treatment (175 mg/day). The donor was an apparently healthy young man who died after brain injury. Eighteen months later, the patient complained of progressive weakness in her legs. In the next 3 months a rapidly evolving paraparesis with bilateral, symmetric pyramidal, sensory, and bladder dysfunction became evident. She was admitted to another hospital. The CSF contained 37 white cells/ml, 93 mg/ml protein, and 43 mg/dl glucose. Serological tests for neurotropic virus were negative. On T2 weighted MRI a diffuse hypeintensity of the cervicothoracic spinal cord was seen. The rest of the data from an extensive investigation were non-contributory. She was transferred to our institution on 3 August 2000. Other than a complete paraplegia no neurological abnormalities were found. Somatosensory evoked potentials after median nerve stimulation were normal but they were abolished after posterior tibial nerve stimulation. In the CSF there were 9 white cells/ml, 133 mg/ml protein, and 43 mg/dl glucose. Serological tests for HTLV 1 (enzyme linked immunosorbent assay) and western blotting were positive in blood and CSF, and the polymerase chain reaction was positive in blood. Tests were negative for HTLV 2 and VIH. The patient received a pulse of methylprednisolone (1 g/3 days) and a course of interferon (3 MU/day/month) without any improvement in her neurological status.

We have conducted a retrospective serological survey for HTLV 1 antibodies in archival blood samples from the patient before the transplantation, from the liver donor, and from the blood donors. All the samples were negative for HTLV 1 antibody from the liver donor. He was a multiorgan donor (both kidneys, liver, heart, and corneas). A follow up of all the recipients is in progress.

The prevalence of HTLV 1 infection in the endemic area of 5%–30% and in western countries it is less than 1%. Despite of this low prevalence, several European countries (France, Holland, Sweden, Denmark, Luxembourg) and the United States have introduced new search for HTLV 1 antibodies in their blood banks. Furthermore, in France the test for HTLV 1 infection is mandatory in all organ donors. In Spain, a serological survey conducted among 23 000 blood donors in 1992 detected only one suspected, subsequently not proved, carrier. Consequently, a routine test for HTLV 1 was not implemented. However, an ad hoc national registry reported 24 cases in Spain up to 1994. Since then, further cases have been found (V Soriano, personal communication).

In Japan, the Japan National HTLV Survey reported that 15 out of 153 recipients of renal transplants were HTLV 1 positive. They did not develop HAM/TSP or any HTLV 1 related disorder during a follow up period of more than 10 years. By contrast, the case we are reporting here indicates that HTLV 1 infection may have devastating consequences for some immunocompromised organ recipients. This emphasises the necessity for a systematic survey of its antibodies in all potential donors despite the low current prevalence of HTLV 1 infection in western countries.

Relation between the high production related allele of the interferon-γ (IFN-γ) gene and age at onset of idiopathic Parkinson’s disease in Japan

Although the pathogenesis of progressive degeneration of nigrostriatal dopaminergic neurons in Parkinson’s disease remains uncertain, cytokines are thought to contribute to the development of the disease. Interferon (IFN-γ) is one of the Th1 cell derived multifunctional cytokines and seems to influence neuronal differentiation and to increase in inflammatory and neurodegenerative diseases. Immunohistochemical studies showed an increase of IFN-γ expression in nigral astrocytes of patients with Parkinson’s disease. This increase of IFN-γ concentration may be a trigger for the disease or a compensatory response. It was reported that IFN-γ producing capacity in whole blood cultures of untreated parkinsonian patients decreased compared with sex and age matched healthy controls. This supports the idea that IFN-γ may increase in Parkinson’s disease as a compensatory response. Concerning genetic polymorphisms in the IFN-γ gene, high production of IFN-γ measured in peripheral blood mononuclear cell cultures may correlate with dinucleotide CA repeat polymorphism in the first intron of the IFN-γ gene.

In vitro production of IFN-γ is higher in
people homozygous for allele 122 (12 CA repeats, named allele 2 by Pravica et al) and allele 6 by Awata et al) than in those of other genotypes. Therefore, we investigated the CA repeat polymorphism of the IFN-γ gene in 170 patients with idiopathic Parkinson's disease (102 women and 68 men, aged 42 years (SD 9.7) years; onset, 55.5 (SD 10.6) years; disease duration 8.7 (SD 5.2) years). As controls, 157 healthy people were selected from the annual health examination at a city clinic. The control group was matched with the patient group by sex, age (mean: 62.5 (SD 8.7) years), sex ratio (98 women and 59 men), and birth place (Kyoto and Osaka prefectures) with the patients. All participants were Japanese. The study protocol was approved by the institutional ethics committees and informed consent was obtained from every participant. The CA repeat polymorphism was analyzed according to a genetic protocol. In patients with early onset disease, allele 122 carrier frequency in patients with early onset Parkinson's disease was also shown to be low allele 122 carrier IFN-γ concentration and in controls, the p value was obtained by multiplying the p value by two. No significant difference was found between patients with early onset Parkinson's disease and controls (p=0.23) or between those with late onset Parkinson's disease and controls (p=1.17). However, the allele distribution was significantly different between early onset (<50 years) and late onset (≥50 years) disease (χ²=4.62, df=5, p=0.028). The frequency of allele 122 was lower in those with early onset Parkinson's disease than in those with late onset Parkinson's disease. Carrier analysis also showed a low allele 122 carrier frequency in patients with early onset compared with late onset disease (χ²=4.62, df=1, p=0.039). Although the genetic polymorphism of IFN-γ does not seem to be a risk factor for Parkinson's disease, a lack of high producer alleles 122 may affect the onset of disease. The allele 122 may be a part of a haplotype that also includes functionally relevant polymorphisms. Our findings support the idea that the increase of IFN-γ concentration in the brain of patients with Parkinson's disease would be lower in those with lower onset rather than a trigger of the disease. Thus, IFN-γ might be helpful in delaying the progress of the disease.

Table 1 IFN-γ allele and carrier frequencies in patients with Parkinson's disease (PD) and in healthy controls as well as in patient subgroups whose ages of onset are early (<50 y) and late (≥50 y).

<table>
<thead>
<tr>
<th>Allele (bp)</th>
<th>PD n (%)</th>
<th>Control n (%)</th>
<th>Early onset PD n (%)</th>
<th>Late onset PD n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>116</td>
<td>1 (0.3)</td>
<td>1 (0.3)</td>
<td>1 (1)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>118</td>
<td>2 (0.6)</td>
<td>2 (0.6)</td>
<td>2 (1.8)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>120</td>
<td>52 (15.3)</td>
<td>51 (13.1)</td>
<td>23 (23)</td>
<td>29 (12.1)</td>
</tr>
<tr>
<td>122</td>
<td>157 (46.2)</td>
<td>143 (45.5)</td>
<td>35 (35)</td>
<td>122 (50.8)</td>
</tr>
<tr>
<td>124</td>
<td>19 (5.6)</td>
<td>16 (3.1)</td>
<td>8 (8)</td>
<td>11 (4.6)</td>
</tr>
<tr>
<td>126</td>
<td>24 (7.2)</td>
<td>22 (6.7)</td>
<td>28 (28)</td>
<td>65 (27.1)</td>
</tr>
<tr>
<td>128</td>
<td>9 (2.6)</td>
<td>8 (2.5)</td>
<td>1 (1)</td>
<td>8 (3.3)</td>
</tr>
<tr>
<td>130</td>
<td>1 (0.3)</td>
<td>1 (0.3)</td>
<td>1 (1)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>132</td>
<td>6 (1.8)</td>
<td>6 (1.8)</td>
<td>3 (3.2)</td>
<td>3 (1.3)</td>
</tr>
<tr>
<td>Total</td>
<td>340</td>
<td>314</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>

For combined alleles 116, 118, 130, and 132, allele frequency: early onset PD ≤ 0.62, df=5, p=0.028.

Carrier frequency: early onset PD ≤ 0.62, df=4.62, df=1, p<0.003.

This work was supported in part by grants in aid from the Ministry of Health and Welfare of Japan (Health Science Research Grants, Research on Brain Science and a grant in aid for Neurodegenerative Disorders).

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**Autonomic dysreflexia due to neurogenic bladder dysfunction; an unusual presentation of spinal cord sarcoidosis**

Clinical involvement of the CNS in sarcoidosis is seen in about 5% of patients. The most common affected sites are the basal leptome- ninges and the region of the floor of the third ventricle. However, primary involvement of the spinal cord is much less common. It may cause serious neurological deficits below the affected level of the lesion. Here we describe a case of spinal cord sarcoidosis with an unusual presentation: autonomic dysreflexia due to neurogenic bladder dysfunction.

A 42 year old woman began to have a slowly progressive spastic gait, left hand numbness, urinary urgency/frequency, and voiding difficulty which worsened over a year. She underwent C2–7 laminoplasty for a relief of C4–6 cervical disc herniation where mild cord swelling was present. However, her gait difficulty ameliorated only for 2 weeks. Two months later she became unable to walk without an aid. Spinal MRI disclosed C2–7 cord swelling. She developed bilateral hilar lymphadenopathy, ocular uveitis, and an increased serum concentra tion of angiotensin converting enzyme (ACE). Endoscopic lymph node biopsy showed non-caseating epitheloid granuloma. These findings and the clinical features confirmed the diagnosis of spinal cord sarcoidosis. She underwent steroid pulse therapy (1000 mg/day of intravenous methylprednisolone over 3 succeeding days) and started taking oral prednisolone (80 mg/day) with benefit. Steroids were tapered to 40 mg every other day and 4 months and then referred to our hospital. However, her gait difficulty relapsed together with urinary urge incontinence and voiding difficulty. She had constipation but no other orthostatic hypotension. On admission to our hospital, she was treated with a tetraparesis, which was dominant in the legs. Deep tendon reflexes were brisk with Babinski's signs. Sensations for pin prick and proprioception were decreased bilaterally below the C6 dermatome. Routine laboratory data were normal. Examination of CSF showed normal cell count (lymphocyte 1/mm³) but mildly increased protein content (42 mg/dl). The ACE concentration was normal both in the serum and CSF. Spinal MRI disclosed C2–7 cord swelling which appeared as low signal intensity on T1 weighted images and high signal intensity on T2 weighted images (fig 1). Gadolinium-DTPA images showed contrast enhancement in the C4–5 intramedullary region which extended longitudinally through the surface of the spinal cord. She again underwent three courses of steroid pulse therapy and started taking oral prednisolone (40 mg/day) and cyclosporin (200 mg/day), which gradually ameliorated her neurological symptoms.

However, she began to have a sudden onset of severe, throbbing headache twice a week which was accompanied by conjunctival congestion, facial flushing, lacrimation, and congestion of the nose, without evidence of skeletal muscle spasms or bowel contraction. Just before the attacks she felt only slight bladder sensation. Measurement of the blood pressure showed an extreme hypertension (190/100 mm Hg) without increasing heart rate (60 beats/min), although it showed a normal value between these attacks. On the first attack emergent brain CT disclosed no subarachnoid hemorrhage and 5 mg of sublingual nifedipine was applied. Autono mous dysreflexia was suspected and the bladder was catheterised, which showed a postvoid residual urine volume of 650 ml. These treatments ameliorated all of her symptoms and the hypertension within 30 minutes. We performed urodynamic studies which showed voluntary voided volume of 79 ml with low maximum and average flow rates. She had a postvoid residual volume of 350 ml (normal<30 ml). On EMG-cystometry, the first sensory stimulation was 350 ml (normal 100 ml) and the maximum bladder capacity was 980 ml.
670 ml (normal 200 ml–600 ml), indicative of impaired bladder sensation. A detrusor hyperreflexia was noted at the end of bladder filling. When asked to void after the detrusor hyperreflexia, her detrusor pressure increased slightly with poor urinary flow although the rectal catheter was pulled off at the end of voiding. There was no detrusor–sphincter dyssynergia. In the pressure-flow analysis the point of a detrusor pressure (Pdet) at a maximum urinary flow rate (Qmax)—that is, PdetQmax—indicated equivocal obstruction (Abrams-Griﬃths’ nomogram) and normal detrusor contraction (Schäfer’s nomogram). Above results indicated the presence of neurogenic bladder dysfunction. To avoid bladder distension, she was taught clean intermittent self catheterisation and started taking oral prazosin hydrochloride, a selective α1-antagonist, which may account for the amelioration of both autonomic dysreflexia and neurogenic bladder dysfunction in the patient.

was taught clean intermittent self catheterisation and started taking oral prazosin hydrochloride, a selective α1-antagonist, with beneﬁt. During autonomic dysreflexia, concentrations of plasma noradrenaline (norepinephrine) increase and other substances—such as neuropeptide Y—may also increase in certain regions. The bladder neck (internal urethral sphincter) is innervated by sympathetic nerve and abundant with α1A/D-adrenergic receptors. The α1-antagonists relax both vascular (mainly α1B) and urethral (mainly α1D) smooth muscles, which may account for the amelioration of both autonomic dysreflexia and neurogenic bladder dysfunction in the patient.

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Figure 1 MRI of the spinal cord (sagittal plane). (A) T2 weighted images, (B) T1 weighted images with gadolinium enhancement. MRI disclosed C2–3 cord stenosis. The intramedullary region of the stenosed cord was low on T1 weighted images and high signal intensity on T2 weighted images. Gadolinium-DTPA images showed contrast enhancement in the C4/5 intramedullary region which extended longitudinally through the surface of the spinal cord.

CORRESPONDENCE

The late whiplash syndrome: a biopsychosocial approach

In their admirable review, Ferrari and Schrader re-introduce the biopsychosocial model which recognises that the late whiplash syndrome is not the result of a chronic injury. They note the influence of compensation incentives such as that seen in Switzerland and other western countries. It is the high percentage of patients with chronic pain attributed to accidents that provide the greatest health care and economic burden.

The biopsychosocial model considers an eff ects of cultural expectation, cultural factors that generate symptom amplification and attribution. I agree with their conclusion that it negates the concept of “chronic injury” but at the same time takes away the stigma of the psychiatric label, while explaining that people’s behaviour in response to their injury may generate much of the illness. The authors surprisingly neglect the final mechanism of the symptoms so often claimed in medicolegal practice, but so seldom encountered in the hospital clinic. They seem to blame cultural expectations and society at large, but they fail to consider the “victim”,
who stands to gain sums of money, often
to the £ of others. The social and cultural factors
they so well describe are real, but the produc-
tion of symptoms’ ultimately depends on the
conscious will of the claimant in providing a
discriminating narrative of their injury, duration, and the
consequent disabilities and loss of earnings. In
litigation practice, deliberate exaggeration is
common. It is misleading to inculpate society alone, and insisting
the patients or claimants to deny their exercise of free choice.

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1 R Ferrari, Schneider H. The late whiplash syndrome: a biopsychosocial approach. J Neu-
2 Ferrari R, Kwan O, Russell AS, et al. The best
approach to the problem of whiplash? One
ticket to Lithuania, please. Clin Exp Rheumatol
3 Pearce JMS. The myth of chronic whiplash
4 Ferrari JMS. A critical appraisal of the chronic
whiplash syndrome. J Neurol Neurosurg Psy-
Cognitive complaints in patients after whiplash
injury: the impact of malinger. J Neurol Neurosurg
Psychiatry 1998;64:33–43.
6 Landy PJ. Neurological sequelae of minor
206.

Ferrari replies:
Pearce’ completes the biopsychosocial mod-
el(s) of whiplash by recognising factors that
we could not, for lack of space, include, although
they have been discussed in detail elsewhere. Illness behaviour is the end result
of many factors, including pathophysiological
processes, experience biased interpretations
of many factors, including pathophysiological
motivations, and so forth. Thus, we gather most whiplash patients are
victims, not so much of the collusion, but of a
system that endangers their health. It is
further clear that the day has come to view
the whole beast that is whiplash. Researchers
that assert that psychosocial factors do not
primarily determine the outcome of illness
behaviour in patients with whiplash, or that
the primary determinants are to be found in
the microscopic nature of the cervical spine
are simply too wrong to be given any further
credence or consideration. There are so
many “facets” to whiplash, that the whiplash
injury itself becomes of less importance when
we desire to understand the larger range of
illness behaviour, and why it evolves.

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1 Pearce JMS. The late whiplash syndrome: a
biopsychosocial approach. J Neurol Neurosurg Psy-
2 Ferrari R. The whiplash encyclopedia. The facts
and myths of whiplash. Gaithersburg, MD:
3 Plöwsky I. Abnormal illness behaviour. Chichester:
4 Ferrari R, Kwan O. The no-fault flavor of
disability syndromes. Med Hypotheses 2001;56:
77–84.

CORRECTION

Kalamangalam GP, Ellis SJ. Migrainous
brain stem disturbance in Norrie disease: case

Chen ZY, Denney RM, Breakefield XO. Norrie
disease and MAO genes: nearest
was misquoted in the second sentence of
paragraph 8 of the above letter. The sentence
should read “The gene is flanked by the
MAO-A and MAO-B loci”.

NOTICE

British Neuropsychiatry Association 2002 Annual
Meeting
21/22 February 2002

The British Neuropsychiatry Association 2002 Annual Meeting will be held
at the Institute of Child Health, central London on 21/22 February 2002.

The meeting will cover four topics:
“Clinical and Neurobiological aspects of new variant CJD”
“The Mind’s Ear”
“Pervasive Developmental Disorders”
“New Drugs for Neuropsychiatry”

The meeting includes keynote addresses from prominent international and
United Kingdom speakers, along with a session for members’ contributions.

For further information please contact: Gwen Cutmore, BNPA Confer-
ence Secretary, Landbreach Boatyard, Chelmer Terrace, Maldon, Essex.
CM9 5HT, (tel/fax: 01621 843334; email: gwen.cutmore@lineone.net,
website: www.bnpa.fsnet.co.uk).

For details of membership to the BNPA, open to medical practitioners in
psychiatry, neurology, and related clinical neurosciences, please contact: The
Secretary, Professor A S David, Department of Psychological Medicine,
Institute of Psychiatry, De Crespigny Park, Denmark Hill, London SE5 8AF.

www.jnnp.com
BOOK REVIEWS


This book claims to examine objectively the basic pharmacological and clinical aspects of the use of benzodiazepines. The agenda is clearly laid out in the introduction where the editors emphasise that the valuable use of these compounds in neurological disorders was overlooked because of the “political turmoil and confusion about the use of benzodiazepines in psychiatry”. In practice the book primarily sets out to make the case for benzodiazepines as acceptable pharmacological treatments for epilepsy, with seven out of 13 chapters devoted to this specific topic. The consensus statement in the introduction suggests that the origins of the publication were a workshop organised by the editors on the use of benzodiazepines in epilepsy, although this is not explicitly stated. Clearly, the balance of the book is heavily weighted towards the treatment of epilepsy and as such this is not a little misleading. This is not a book for the general physician or psychiatrist looking for an overview of the clinical pharmacology of benzodiazepines. The first five chapters examine the pharmacological properties of benzodiazepines, their amnestic properties, and their utility in the management of anxiety and sleep disturbance. These are not all written with equal objectivity. The chapter on the management of sleep disorders delivers a clinically relevant and balanced review and includes ecletic, practical advice. By contrast, the chapter on the use of benzodiazepines in anxiety disorders focuses on these compounds to the exclusion of other interventions. Whereas the potential problems of tolerance and dependence are acknowledged, the problems of cognitive and psychomotor impairment, which are discussed in a previous chapter, are not. There is also little mention of SSRI antidepressants, despite their proved efficacy in anxiety disorders and limited discussion of the relationship between drug and non-drug treatments. The epilepsy chapters present short expert reviews of specific clinical indications for benzodiazepines with some new pharmacoeconomic data. In summary, this is a really a specialist text with a general title that is most relevant for and likely to be read by clinicians treating patients with epilepsy.

CHRISTOPHER BENCH


Stem cells, like the ancient Chinese ruyi sceptre, mean different things for different people. For doctors and patients they are a future gold mine and a haven from the dot com carnage. But for the scientists working with them, well, the scientists are not quite sure what stem cells are. Some chapters in MS Rao’s edited collection “Stem cells and CNS development” attempt a definition of a “true” stem cell but like fragments of the True Cross, they are elusive. Stem cells should be capable of infinite division (but stopping just short of immortality), reproducing themselves, as well as give rise to all the differenitated specialised progeny, remaining quiescent until required, and capable, when transplanted, of recognising exactly what tissues are lacking or diseased, turning into (and into) the right numbers, migrating to the required area, and incorporating themselves into new, now fully functional host tissues.

Is there a neural stem cell, analogous to the haemopoietic stem cell? The progeny of a haemopoietic stem cell only have to be released into the circulation. If we can find a source of neural stem cells, can their progeny be expected to incorporate equally easily into the immensely complex and variable nervous system? Will we be able to discover the factors needed to drive stem cell differentiation in the directions needed to produce the specific progeny required for a particular application? It is too early to know if and how play in the practical application of haemopoietic stem cells is anything to go by, we may have to wait a while before neural stem cells will be curing diseases.

The reader will find all these topics dealt with in Rao’s compendium. It is fully referenced, and provides a comprehensive and valuable snapshot of where things are now. Hopefully, the reader’s copy will not like this copy review review copy, have 15 pages missing, and seven duplicated.

GEOFFREY RAISMAN

Maudsley neuropsychiatry modules: a teaching package for self paced learning or small group seminars. By STEVE CHURCH (includes a workbook, videotapes, and a reference textbook) (£250.00). Published by Maudsley Publications, 2001 ISBN 0 9502289 8 3.

It is difficult to think of any medical book that has done so much to raise the profile of a specialty as Organic Psychiatry by Alwyn W Lishman has done for neuropsychiatry. The third edition of Organic Psychiatry, published in 1997, will remain a classic for many years to come. Its focus on the clinical description of neuropsychiatric syndromes and the clarity and elegance of the writing will ensure that. It is a tribute to the book that, as in the cases of popular literary works, a film should be based on it, or in this case two videos, a workbook, and an answer book. By contrast with the Hollywood tradition that renders the book of the film obsolete, this teaching package requires the reader to go back to the original source to get the best of the other components of the package.

The package, which also includes the Organic Psychiatry book, is described as a teaching resource in neuropsychiatry for self paced learning and is aimed at English speaking students. The text book and videotapes contain seven modules: examination of the neuropsychiatric mental state, investigations (EEG, imaging, and neuropsychology), head injury, epilepsy, infection, dementia, and movement disorders. The various modules are introduced by Professor Goldberg, who introduces the contributing neuropsychiatrists, in a setting somewhat reminiscent of Bird and Fortune, emphasising the importance of taking a careful history and making a differential diagnosis. The workbook provides a brief background to these modules and directs the student to the Lishman for further reading and to the relevant section of the video. After each module the student is invited to answer questions and feedback is provided in the workbook.

We are warned that the modules do not provide exhaustive coverage, as they have been selected for their relevance. However, the course seems rather idiotic and I suspect that it must have been dictated to some extent by the availability of patients. The package is a team effort and many well known neuropsychiatrists are seen interviewing patients in the workbook, case of Professor Lishman, demonstrating the neuropsychiatric examination on a normal subject. To assemble and edit all the clinical material contained on the tapes must have been a considerable, but worthwhile, effort and I hope the student to go over these vignettes for the interests of the clinical cases. All modules contain interesting material, but I particularly enjoyed the first two (examination of the mental state and consciousness), because they are more exhaustive in their coverage than anything that follows and the many examples of abnormal mental states provided blend particularly well with the demonstration of the neuropsychiatric examination. It is a pity in other modules that abnormal investigations are not shown alongside the clinical interviews. It would have been appropriate for example a CD of imaging of patients with frontal lobe syndromes or Alzheimer’s disease and the EEGs of the various epileptic patients interviewed. Abnormal examples of imaging and EEGs appear in the workbook, but are not always related to the clinical material on the tapes.

All in all, this is a very valuable teaching package for trainees in different areas of clinical neuropsychiatry, but particularly useful for those with technology, the publishers will consider producing a CD Rom version in the future.

M A R I A A R O N


Post-traumatic stress disorder (PTSD) did not enter the psychiatric lexicon until 1980 when the American Psychiatric Association’s DSM-III proposed operational diagnostic criteria for the condition. Nevertheless, it is clear from previous descriptive studies that the symptoms which are now associated with PTSD were often and consistently recognised in victims of trauma, particularly involving military conflict. The impetus to the establishment of PTSD as a diagnostic concept came from studies on veterans of the Vietnam war. Since the 1980s there has been a steady growth in the frequency with which PTSD is diagnosed, facilitated by a broadening of the diagnostic criteria, particularly the nature of the precipitating aetiological trauma. Several sceptics have also noted the increased tendency to diagnose the condition to a growth in the
Trade in litigation, actively promoted by the legal profession. The popularity of the diagnostic concept has been matched by an explosion of published papers, so this book is a timely review which enables clinicians and lawyers to keep up advances in understanding the aetiology and management of the condition. Like most multi-author books the quality is uneven and there is some overlap between several chapters. The strength of the book lies mainly in the chapters on treatment. There are useful contributions from Barbara Rothbaum on psychological treatments and from Stein et al on pharmacotherapy. There is also a very good article by Martin Dewitt on psychological debriefing. This has become a popular form of intervention after trauma but its effectiveness is uncertain and at present its widespread use cannot be justified. More research needs to be undertaken to identify victims who are likely to develop PTSD and to distinguish them from those who are more resilient and who do not require any form of psychological intervention.

This book is a useful, up to date, and comprehensive summary of the current state of knowledge on PTSD. It deserves to be widely read by neuropsychiatrists, clinical psychologists, and personal injury lawyers, all of whom are likely to be consulted by a growing number of victims of trauma.

GEOFFREY LLOYD


This multi-author book aims to improve the management of patients with spasticity in two ways. It provides a clear and clinically relevant account of the underlying neurophysiology that will help clinicians understand the nature and genesis of the problem. And it provides a critical and up to date review of much of the relevant clinical evidence. Large parts of the book are weak, but this book will not mislead and is good value for money.

One weak area in the book is the coverage of the measurement of spasticity. There is one chapter devoted to the topic, by one of the editors, yet this chapter does not make any reference to the Tardieu scale, which forms an important part of the next chapter on physiotherapy management. The next edition should ensure at least adequate cross reference. There is little discussion of the indirect measurement of spasticity, measuring the consequences of spasticity such as reduced range of movement, pain, frequency of spasms, or the difficulty experienced by carers in activities. It is these measurements which are being used in modern trials. It would be helpful to include a review of measures of the management of spasticity, especially because this will be the main clinical interest in measurement.

Two excellent chapters cover the explanation of the neurophysiology and the pharmacological management of spasticity. Both draw heavily on evidence which is heartening. High quality evidence is lacking in many other areas, but the discussion of matters such as seating and the use of intrathecal baclofen does draw on experience, and is clearly written. In practice most clinicians will need to learn from direct experience, but if good teachers are not easily available then this text will give a good start to the learning curve.

Some chapters do not use all the evidence that is available. The chapter on orthoses focuses too much on being a catalogue of available orthoses, with only a critical evaluation of their utility. The chapter on chemical neurolysis similarly lists and describes the various anatomical options. There are certainly studies, including a large randomised controlled trial from The Netherlands that investigate the use both of orthoses and neurolysis and this study is not referenced. There are several studies investigating the use of ankle-foot orthoses.

Finally there is a good chapter on the use of botulinum toxin, its only and invariable weakness being that some studies are omitted because more evidence is being published regularly. However, it is sensible and accurate and will be a sound basis for action in most cases.

In summary this book covers almost all aspects of spasticity that doctors, therapists, nurses and other clinicians may be interested in. Its use of evidence is good, although it could be improved. It cannot substitute for being taught by someone with experience, nor can it substitute for keeping up to date through continuing professional development but if spasticity management is only a part of your workload (rather than being your specialty) then this book will give a good foundation for clinical practice for the next few years.

DERICK WADE


It was not so many years ago that a diagnostic approach to dementias was limited to the exclusion of potentially reversible causes. It is becoming increasingly clear that clinicians now need to be able to differentiate not only between reversible and irreversible causes but also between the primary degenerative dementias themselves. The past decade has seen great advances in our understanding of the basic science of the dementias, particularly Alzheimer's disease, bringing us not only a theoretical basis for different symptomatic conditions in different dementias, but also the promise of future therapies that may act directly on the molecular underpinnings of these diseases.

If clinicians are to be able to make these clinical distinctions and initiate appropriate therapy, then unless they are neurologists with a specialist interest in dementias, they may need a little help. Robert Green's book, Diagnosis and management of Alzheimer's disease and other dementias, provides that help and a whole lot more. Although in its introduction Dr Green claims that his manual is aimed at the primary care physician it is also informative and useful enough to provide considerable benefit to neurologists in training and neurologists whose roles are specialisation lies outside the realm of dementias.

One of the greatest difficulties in reviewing this publication has been to find what was missing. For several weeks this volume has been carried around in my briefcase with regular checks to see if it included certain aspects of the management of dementing illnesses. From the appropriate dose of vitamin E, the debate on the use of ginkgo biloba, the use of CSF biomarkers in diagnosis, to advice on handling the emotionally charged issue of driving, each time, this small book was informative.

Essentially, the book is divided in four parts. The first, on general aspects of dementing disorders, opens with definitions and the epidemiology of dementias. The following section on the evaluation of the older patient with cognitive problems emphasises issues such as the importance of taking a corroborative history, and the assessment of functional capabilities or activities of daily living. The appropriateness of ancillary investigations such as neuroimaging, neuropsychology, CSF analysis, and electroencephalography are discussed as well as aspects of a bedside mental status examination. If I had one minor quibble it would be the absence of instructions for a new and useful test of neuropsychological function that can be used at the bedside. Although we all know that we should assess short term memory, few of us can administer a simple list learning task at the bedside or in the clinic. The book concludes with a chapter on cognitive disorders not due to Alzheimer's disease and is particularly useful in detailing the differentiation of Alzheimer's from delirium, depression, frontotemporal dementia, and dementia with Lewy bodies.

Part two of the book is devoted to Alzheimer's disease, its genetics, natural history, neuropathology, and management options. In the third part, practical and behavioural issues are addressed and it is here that we really benefit from the experience accumulated by Dr Green and his team in Boston in caring for many patients and their families through the course of these devastating illnesses. The final section of the book is devoted to resources for clinicians and families, over 400 references, and a comprehensive index.

In summary, on the basis of its content, this book is well written, well structured, comprehensive, and above all useful. For me however, its strongest feature is that it was all this into a slim volume measuring only 19 x 10 cm, which was easily carried around in my case.

RICHARD PERRY


David Kline and Alan Hudson wrote Nerve injuries, a work of exceptional importance which was published in 1995. In this work they joined by Daniel Kim and present an atlas of operative exposure with a discussion of methods of repair of nerves; this is a companion volume to the earlier work.

Nineteen chapters describe the anatomical relations of the peripheral nerves in the upper and lower limb, of the brachial plexus, of the intrapelvic course of the femoral and sciatic nerves, and of the nerves of the abdominal wall. Five chapters describe methods of nerve transfer or of nerve repair, a further chapter is dedicated to neurolysis, one

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chapter is dedicated to intraoperative neurophysiological work, and there is chapter dedicated to technical questions for the treatment of nerve sheath tumours.

There is a lengthy appendix, of some 100 pages, with photographs of anatomical dissections. These, from Dr Kim, are of the highest quality.

This work is more than a surgical companion. The detailed description of the relation between peripheral nerve trunks and adjacent axial structures, the relation of anatomical variation makes it relevant to any clinicians engaged in the diagnosis of patients with disorders of peripheral nerves most especially to those inclined towards interventional work. The descriptions of the course and relations of nerves of cutaneous sensation in the lower limb and of the nerves of the abdominal wall is particularly good and of direct relevance in the treatment of patients who have had accidental damage to those nerves. Too often these patients present with severe pain, and, because of ignorance, the importance of the distribution, and the location of those sensory disturbances, inappropriate treatment is commenced.

The careful description of the exposure for operations of thoracic outlet syndrome serves to remind all of the potential seriousness of this procedure. I particularly liked the chapters describing exposure of the suprascapular and the circumflex nerves, of the course and variations of the sciatic and of the femoral nerves and most especially the account of David Kline’s own operation, the posterior or subscapular approach to the most proximal segment of the spinal nerves passing to the brachial plexus and upper limb. Of the technical chapters describing intraoperative compound nerve action potential recordings, a particular contribution from David Kline is especially good.

The work is greatly enhanced by Dr Kim’s photographs of dissections. This is important and valuable work, I would suggest that it is essential reading for surgeons engaged in this work but that its interest extends well beyond that group. There are inevitably errors which will require attention when the work comes to revision, figure 1.11 does not demonstrate the correct relation of the spinal accessory nerve to the uppermost spinal nerves, figure 13.8 showing the course of the posterior interosseous nerve requires attention. Set against the whole these are very minor blemishes.

The authors are to be congratulated on producing an important book which does indeed act as a “companion surgical dissection text or atlas” to their earlier work, which in fact goes well beyond.

ROLFE BIRCH