LETTERS TO THE EDITOR

Fear can interrupt the continuum of memory

I had always thought that the existence of post-traumatic amnesia, characterised by gaps in the patient's memory of events after an accident, particularly if the remaining "snapshots" of memory were particularly vivid, meant that the patient must have been knocked out, albeit briefly. I had always rejected the concept that fear, acute anxiety, panic, that which the layman calls "shock", could be responsible for the phenomena of post-traumatic amnesia. That is until about 6 months ago.

I was driving in the wet, too fast, in a convoy in the outside lane. The conditions were appalling; I was alert. Six or seven cars in front of me were involved in a "front to rear shunt", precipitated by a car that had been stuck on the inside lane behind a slow moving vehicle, darting without warning into the outside lane.

I remember seeing this car do this, I have a vivid image of seeing a car, perhaps two away from me, suddenly appearing at right angles—I could see its rear end to the left of, and the front end to the right of the car in front of me. I have no recollection of putting my brakes on, and then I have a very clear image of the car in front of me coming towards me as I skidded. This was a crystal clear isolated image, associated with an absolute conviction that I was about to die—the car was a small red Honda saloon, the front passenger was wearing a flowery hat, and there was a black and white soft toy dangling in the rear window. I have no recollection of avoiding this car, or steering or skidding to the offside, I have no recollections until that of my car slithering to a bumpy halt on the grass verge at the central reservation of the road. I remember thinking that the antiskid mechanisms had not worked. My next recollection is of looking down through my opened door (without any memory of opening it) at the thick mud of the central reservation and thinking that I would have to clean my shoes after walking on it. At that point clear and continual memory is restored and I went to see if I could assist the people in the other cars, and eventually I drove off.

As I continued on I ruminated on events, and realised that there was no doubt about it—there were significant blanks in my memory of events, and that furthermore those memories I did have were extremely vivid—the hat, the dangling toy, the sure fire knowledge that I was about to die, and the light brown slimy mud on the central reservation.

There is no question at all of my having hit my head, or being subjected to any violent to and fro acceleration or deceleration forces—this was peritraumatic amnesia in which the trauma was wholly psychological.

I am grateful to my anonymous referees for drawing my attention to two reviews—by van der Kolk and Fislér¹ and by Kopelman²—on the subject of psychological trauma and amnesia. Neither papers describe precisely what I am describing and neither accentuate what to me is a most remarkable phenom-

enon and that is the very vivid nature of these memories. Now, 6 months later, some of the memories are beginning to fade, but interestingly it is not the conviction of impending death that persists but it is the image of the mud. This vivid nature of post-traumatic amnesic memories was described by Russell and Nathan.³ I think that this is what differentiates my experience from a dissociative state—although I am obviously open to correction on this.

In answer to the inevitable question from my fellow medicolegal report writers—no I did not develop any of the features of "post-traumatic stress disorder".

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Folate in CSF and age

Low serum and red cell folate concentrations have been reported in up to 42% of elderly healthy subjects in the community or acute geriatric medical admissions, and in 20%–82% of psychogeriatric admissions.¹ Although widely attributed to dietary causes, we have long reported a causal link between folate deficiency, depression, or dementia.¹⁻³ Recent community studies have suggested a significant rise in serum total homocysteine and fall in serum folate with age⁴; and there has been renewed interest in a link between Alzheimer's disease, depression, folate deficiency, and raised serum total homocysteine.^{5,6} Other studies suggest that high homocysteine and low folate concentrations are independent risk factors for premature occlusive vascular disease, including cerebrovascular disease.^{4,5}

Remarkably, folate in the form of methyl folate is concentrated in CSF by an active transport process at concentrations about three times that in serum.³ We have had the opportunity to study CSF folate in a group of elderly patients undergoing spinal anaesthesia.

Folate in CSF was measured in 41 patients undergoing surgery at Northwick Park Hospital in a study of spinal anaesthesia and postoperative spinal analgesia by the Department of Anaesthetics. The operations were hip replacement (22), knee replacement (four), hernia (eight), haemorrhoids (three), and varicose veins (four). There were 17 men and 24 women, mean age (SD) 74.6 (13.4) years. The patients were otherwise healthy and were not taking medication other than analgesics before surgery.

With informed consent, 2 ml CSF were withdrawn at L3/4 in the fasting recumbent position under local anaesthetic before spinal anaesthesia, and was immediately stored at -70°C. Folate in CSF was measured by microbiological assay using a chloramphenicol resistant strain of *L. casei*.

The figure shows a highly significant decline in CSF folate with age. The mean CSF folate (28 (SD 7.4) µg/ml) between ages 40 and 59 fell 5% between age 60 and 69 (26.6 (SD 8.1) µg/ml). The greatest fall was

Relation of age to CSF folate concentrations in elderly surgical patients.

after the age of 70, with a 27% fall between 70 and 79 (20.3 (SD 5.8) µg/ml) and a 54% fall between 80 and 99 (13.0 (SD 5.4) µg/ml). (analysis of variance (ANOVA) $F=11.73$, $p<0.001$). The correlation between age and CSF folate was -0.72 ($p<0.001$).

Our findings provide further evidence of a link between folate concentrations and age and, for the first time, directly in the nervous system. Although we did not measure serum folate concentrations, others have already reported a fall in serum folate and rise in plasma homocysteine with age.⁴ Our subjects were not anaemic or macrocytic and were not known to have medical or psychiatric disorders. It is unlikely, therefore, that the significant decline in CSF folate can be attributable simply to dietary deficiency. Other possibilities include a gradual failure with aging of the active transport mechanism which carries methyl folate into the nervous system.³

Whether due to aging or acquired deficiency, there is evidence causally relating folate status to mental function, especially depression and dementia.^{1-3,5,6} Controlled and uncontrolled clinical trials suggest a specific effect of folate on mood and cognitive function.¹⁻³ The effects of folate on mental function are mainly mediated through numerous methylation pathways in the nervous system and are similar to the effects of S-adenosylmethionine (SAM), the major methyl donor in the brain which obtains its methyl group mainly from methyl folate.¹

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Anterior superior alveolar neuropathy: an occupational neuropathy of the embouchure

A 31 year old French hornist was referred for evaluation of a 9 month history of pain in her right upper lip.

A member of a major symphonic orchestra, she regularly played 4-6 hours a day. Her symptoms began after a heavy period of playing, with a sensation of excess pressure in the right upper lip followed shortly thereafter by frank pain in this area. She spontaneously distinguished between two types of pain. The first was a constant dull ache, extending from the midline 1 cm laterally onto the vermilion lip. She noticed that brushing her teeth or eating could trigger pain in this region. Her second pain sensation was different from the first—electric, lancinating pain originating in the medial portion of the right lip and extending to her right nostril. There were no paraesthesias of the lips, cheeks, or jaw, and she had no symptoms of facial weakness.

She compensated for her difficulties and maintained her usual high level of professional performance. Briefs periods of rest produced temporary improvement; however, her symptoms recurred when she resumed performing. There were no other complaints and her family history and medical history were unremarkable.

Except for her right lip, neurological examination was normal including careful sensory evaluation of the anterior teeth, gums, and palate. Her right first incisor was noted to protrude slightly in front of her left. As shown in the figure, light touch sensibility was reduced in the right lip (wide cross hatching). A smaller region (narrow cross hatching) was painful to touch, lying directly over her prominent first incisor and below the contact point for the circular mouthpiece of the horn (fine stippling). Application of viscous lidocaine to the lip temporarily relieved her symptoms. An MRI of the head was obtained, showing no abnormalities along the path of the trigeminal nerve. A brief course of gabapentin at 900 mg/day was ineffective, and she declined further drug treatment. Filing down her prominent right first incisor in combination with 6 weeks of complete rest produced marked improvement in her symptoms. Her sensory loss improved as well, and she was able to return to work.

Musicians who play brass instruments (trumpet, French horn, trombone, and tuba) spend their professional lives perfecting control of the embouchure, the muscles of the lower face, lips, and tongue that control the direction and intensity of airflow into the mouthpiece. The lips and face of a brass

player experience tremendous pressure from the mouthpiece, sometimes sufficient to cause muscle strains or even traumatic tears in the orbicularis oris.¹

This patient's sensory disturbance localised to the anterior superior alveolar nerve. The superior alveolar nerve divides into a posterior, middle, and anterior group. Branches from these divisions form a plexus that innervates the dental pulp, periodontal membrane, adjacent labial and buccal gingiva, and the upper teeth. The posterior, middle, and anterior branches innervate the molar, premolar, and incisor or canine teeth, respectively. Only the anterior superior alveolar nerve travels with the infraorbital nerve to exit through the infraorbital foramen.² In our patient, her prominent right first incisor predisposed a terminal branch of this nerve to focal entrapment by the overlying mouthpiece rim.

Injuries related to occupation are increasingly recognised among performing artists. Focal entrapment neuropathies of the arm have been well described in musicians. This patient shows that similar occupational neuropathies may affect the lips and face. We are aware of two other reports of patients similar to ours.^{3,4} Given that the force exerted on the lips by the mouthpiece of a French horn has been measured to be as high as 50 N, with displacements of the central incisors of up to 180 µm during playing, it is not surprising that these neuropathies occur.⁵

French horn and trumpet mouthpieces are significantly smaller than those of the trombone and tuba, and so mouthpiece forces are concentrated onto a very small lip surface area. We suspect that there are other French horn and trumpet players who have experienced similar symptoms to our patient.

Entrapment neuropathy is a potentially reversible cause of disability in brass players, and should be considered in the differential diagnosis of embouchure dysfunction.

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Clinical and MRI discordance in a case of delayed radiation myelopathy

Delayed radiation myelopathy (DRM) is a rare complication of radiotherapy, especially when the total dose delivered to the spinal cord is less than 50 Gy.¹ From the limited data reported on the radiological features of DRM, typical MRI changes of cord swelling and gadolinium enhancement on T1 weighted images and increased intramedullary signal on T2 weighted images often correlate well with progression of neurological

symptoms. We report a case of DRM in which the clinical features remained static at a level corresponding only to the lower end of the abnormal intramedullary lesion seen on MRI, without radiological evidence of blood-brain barrier breakdown, suggesting that pathological changes to the spinal cord after radiation are not always displayed as visible changes on MRI.

A previously well 71 year old woman presented in December 1997 to the ear, nose and throat department with hoarseness and difficulty swallowing, having discovered a lump in the right side of her neck. Laryngoscopy showed a right pyriform fossa tumour, histologically confirmed as a lymphoepithelioma after biopsy. Staging neck CT showed extensive tumour in the right pyriform sinus and lateral pharyngeal wall with associated lymphadenopathy extending to the thoracic inlet.

Between April and May 1998, she received chemotherapy comprising 5-fluorouracil and cis-platinum. Radiotherapy was started in June 1998 with fields covering the pyriform sinus and neck, anterior supraclavicular fossa, and posterior neck. The calculated dose delivered to the cervical spinal cord was 42.5 Gy in 2 Gy equivalent fractions.

Over the next 4 months, she improved clinically and on review in October 1998 there were no signs of tumour recurrence, confirmed on laryngoscopy. She remained well until November 1998 when she began to notice progressive numbness and weakness spreading proximally up both legs over a period of 6 weeks, such that she was unsteady when walking. Soon thereafter, she developed urinary incontinence and constipation. At this time, cervical and thoracic spine MRI (figure) disclosed cervical cord swelling with a spindle shaped cavity of low signal intensity on T1 weighted images and high signal intensity on T2 weighted images extending from C4 to the upper end of T1. There was no cord enhancement after the administration of gadolinium.

On neurological review in January 1999, she was incontinent of urine and faeces and was able to mobilise only with the aid of a walking frame. There was generalised wasting in both legs with mild reduction in strength of hip flexion, knee flexion, and extension, but no detectable weakness in the arms. There was a loss of spinothalamic sensation below the level of T5 bilaterally, with a subjective feeling of altered sensation in both hands.

Over the ensuing 4 months, her level of disability progressed such that she was unable to walk or transfer independently. Further examination disclosed flaccid paralysis of both legs and minor weakness of the intrinsic muscles of both hands. There was reduced perception of pain and temperature sensation below the level of C8. She commenced hyperbaric oxygen therapy given on a daily basis for 3 weeks but there was no symptomatic recovery.

After a recurrence of her original swallowing difficulties, she was found to have a tumour recurrence in her pyriform fossa at biopsy, with associated lymphadenopathy. No further radiotherapy was given. At last review in February 2000, she had no movement in her lower limbs and marked weakness of the intrinsic muscles of both hands, with preserved power in proximal upper limb muscles. Sensation above the level of C8 was intact.

Diagnostic criteria of DRM as outlined by Pallis *et al*² stated that the spinal cord should

Sensory loss (wide cross hatching), focal pain (narrow cross hatching), and lancinating pain (arrow) are shown overlying a diagram of the lips. Dashed lines indicate the position of the first incisors, and the contact of the french horn mouthpiece with the lips is shown as a stippled circle.

Sagittal T2 weighted MRI showing a spindle shaped area of increased signal extending from C4 to T1.

be included in the irradiated area; the main neurological lesion should be within segments of the cord exposed to radiation; and that other causes for the neurological disorder have been excluded.

Despite the almost syrinx-like appearance of radiation myelopathy on MRI, the clinical presentation of DRM is usually one of progressive rostral spread of sensorimotor symptoms, where the final clinical level usually corresponds to a level well within the boundaries of the length of abnormal signal seen on MRI, typically within 1 year of symptomatic onset.^{3,4} All but one of the reported cases of MRI features of DRM in the literature have shown ring-like enhancement after gadolinium administration, suggesting breakdown of the blood-brain barrier.^{3,4} As yet, there are insufficient data on precise clinical sensorimotor cord levels in relation to MRI appearances (and possible gadolinium enhancement) in the studies of DRM currently published to enable prediction of clinical outcome based on radiological findings at presentation. Our patient's symptoms and signs plateaued at a level which would indicate an upper level of spinal cord damage at C8/T1, whereas MRI showed extensive cord changes from C4 to the upper end of T1. There was no gadolinium enhancement, but T2 weighted images disclosed evidence of marrow change in the vertebral bodies of C1 to T3, suggesting that the lesion was within the irradiated area. Pathological studies in DRM have shown white matter changes of demyelination and malacia, often affecting the lateral and posterior aspects of the cord, with associated vascular changes of fibrinoid necrosis, thrombosis, perivascular oedema, and haemorrhage.¹

The high signal T2 weighted MRI findings with cord swelling resemble those of syringo-

myelia. However, almost all patients with cervical syrinx formation develop marked sensorimotor symptoms or signs in the upper limbs, and a clinical picture of isolated spastic paraparesis is unusual.⁵ The main areas of cord damage after radiotherapy would seem to be the lateral corticospinal tracts and posterior columns from radiological-pathological studies.⁶ Peripheral ring enhancement of the cord after gadolinium administration suggests that the major focus of cord damage or at least blood-brain barrier breakdown does not lie within the central cord regions. Consequently, the central cord swelling seen on T2 weighted images may well represent oedema, produced in response to altered vascular permeability after radiation damage to the vascular endothelium. In direct intrinsic cord compression, this spindle shaped region of cord oedema has limited correlation with clinical signs, as would be suggested by our case. The presence of gadolinium ring enhancement of the cord, missing in our case, serves as a more reliable marker of structural cord damage, but even in its absence, the diagnosis of DRM can be made in a patient with ascending sensorimotor symptoms within months of radiation therapy, where the only clue to radiation damage to the cord is central cord swelling and vertebral body marrow change with increased signal on T2 weighted images. Follow up MRI shows cord atrophy only in the region of previous gadolinium enhancement, correlating with clinical findings.⁷ Our case has shown that the ultimate level of disability cannot be judged from the extent of the T2 weighted central cord changes seen on initial MRI.

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Lack of association between *IL-1A* and *IL-1B* promoter polymorphisms and multiple sclerosis

Multiple sclerosis is an autoimmune and inflammatory disease of the CNS characterised by recurrent destruction of myelin which results in heterogeneous and unpredictable clinical manifestations. Although the factors able to foster the initial changes leading to CNS demyelination in patients with multiple sclerosis are still unknown, a discrete number of genes are likely to predispose to the occurrence of multiple sclerosis and to influence its clinical variables.

Due to the inflammatory nature of the pathogenic mechanisms mediating CNS damage during multiple sclerosis, association studies have been focused on candidate genes coding for immunorelevant molecules. The interleukin (IL)-1 gene cluster (including *IL-1A*, *IL-1B*, *IL-1RN*), located on the long arm of chromosome 2 (2q12-22; OMIM Database of National Center for Biotechnology Information; www3.ncbi.nlm.nih.gov:80/Omim) and polymorphic in different sites, represents a good target for association studies in multiple sclerosis. *IL-1*, in fact, has been detected within multiple sclerosis lesions.¹ Moreover, lipopolysaccharide stimulated peripheral blood monocytes of patients with multiple sclerosis produce more *IL-1α* and *IL-1β* than controls.² Due to the potential involvement of *IL-1α* and *IL-1β* in multiple sclerosis, a genetically determined polymorphic variation in their production may contribute to the occurrence of multiple sclerosis, or modulate its clinical features. Furthermore, we have recently reported the association between the variable number of tandem repeat polymorphism (VNTR) of *IL-1RN* with multiple sclerosis susceptibility and prognosis.³ *IL-1A*-889 and *IL-1B*-511 polymorphic loci are located 375 and 320 kb respectively from *IL-1RN* VNTR. To determine whether a particular allele or genotype of *IL-1A* or *IL-1B* affects occurrence or clinical variables of multiple sclerosis, we performed a case-control association study in a large cohort of patients with multiple sclerosis and age and ethnicity matched healthy controls.

Patients were clinically diagnosed at the multiple sclerosis centre of the San Raffaele Hospital in Milano as affected by clinically definite multiple sclerosis according to Poser's criteria. All patients had a relapsing-remitting course. Genotype frequencies of the *IL-1A*-889 polymorphism were calculated in a cohort of 399 patients with sporadic relapsing-remitting multiple sclerosis (247 women, 152 men; age 37.3 (SD 12); mean age at disease onset 27.3 (SD 9.3)) and 439 healthy controls (151 women, 288 men; mean age 37.6 (SD 10.6)). Gene frequencies of the *IL-1B*-511 polymorphism were calculated in a cohort of 321 patients with sporadic relapsing-remitting multiple sclerosis (203 women, 118 men; mean age 38 (SD 12); mean age at disease onset 27.4 (SD 9.2)) and 403 HC (146 women, 257 men; mean age 38 (SD 10.9)).

IL-1A-889 and *IL-1B*-511 C/T polymorphisms were characterised by polymerase chain reaction (95°C 30 seconds, 55°C 30 seconds, and 72°C 40 seconds; 40 cycles) using genomic DNA and following primers: *IL-1α* FW 5'-AAGCTTGTCTACACCTGAAGTAGGC-3', *IL-1α* RV 5'-TTAATATGAGCCTTCCATG-3'; *IL-1β* FW 5'-TGGCATTGATCTGGTTCATC-3', *IL-1β* RV 5'-GTTTAGGAATCTTCCACTT-3'). Amplified products were digested with restriction endonuclease (NcoI and AvaI).

Statistical analyses were performed with the SAS statistical package (SAS Institute Inc, Cary, NC, USA). The p values were considered not significant (NS) when greater than 0.05. Gene frequencies were compared by χ^2 test with two degrees of freedom. The homogeneity of Kaplan-Meier disease free curves over strata was tested using the rank statistics (log-rank and Wilcoxon tests).

The *IL-1A* and *IL-1B* alleles were in Hardy-Weinberg equilibrium in all populations and their distributions were not affected

Table 1 *IL-1A and IL-1B genotype frequencies in healthy controls (HC) and in patients with multiple sclerosis (MS) as well as in patients with different disease courses (benign and non-benign)*

	MS	HC	Benign MS	Non-benign MS
<i>IL-1A</i> genotype (% (n)):				
CC	47 (189)	45 (198)	43 (39)	52 (56)
CT	45 (177)	46 (203)	43 (39)	43 (46)
TT	8 (33)	9 (38)	14 (13)	5 (5)
<i>IL-1B</i> genotype (% (n)):				
CC	38 (123)	39 (159)	34 (25)	33 (27)
CT	48 (155)	50 (201)	44 (32)	56 (46)
TT	14 (43)	11 (43)	22 (16)	11 (9)

by sex or age (data not shown). We found a similar gene free distribution between patients with multiple sclerosis and healthy controls for both *IL-1A* and *IL-1B* polymorphisms (table) (*IL-1A*: multiple sclerosis *v* healthy controls, $\chi^2=0.5$, NS; *IL-1B*: multiple sclerosis *v* healthy controls, $\chi^2=1.3$, NS).

The possible association between a given *IL-1A* or *IL-1B* genotype and accumulation of clinical burden over time was assessed by comparing two groups of patients with multiple sclerosis differing for their disease outcome and classified as "benign" (patients with a stabilised expanded disability status scale (EDSS) score ≤ 3 after at least 10 years from disease onset) and "non-benign" (patients with an EDSS score > 3 within 10 years from disease onset, table).³ In the case of the *IL-1A* polymorphism, the gene frequency of 91 benign was not statistically different from those of the 107 non-benign patients with multiple sclerosis ($\chi^2=5.9$, NS). As for the *IL-1B* polymorphism, the gene frequency of the 73 benign patients was also similar to those of the 82 non-benign patients with multiple sclerosis ($\chi^2=4.0$, NS).

To assess whether *IL-1A* and/or *IL-1B* genotypes had an influence on the age at onset of multiple sclerosis, Kaplan-Meier disease free survival curves were calculated, plotting the age at disease onset of each patient versus the respective *IL-1* genotype (data not shown). Again, neither *IL-1A* (log rank $\chi^2=3.9$, NS) nor *IL-1B* (log rank $\chi^2=0.72$, NS) genotypes seemed to affect the distribution of the age at multiple sclerosis onset.

A handful of inflammation associated polymorphisms have been shown to positively associate with the occurrence of multiple sclerosis or to influence its clinical variables, including polymorphisms located within or nearby the HLA locus (important for multiple sclerosis susceptibility), or the *IL-1RN*, *IL-4* and *IL-1B* genes¹ (possibly important in modulating the course of disease).

Our analysis could not demonstrate any association between these two previously untested *IL-1A* and *IL-1B* promoter polymorphisms and the occurrence of multiple sclerosis, the age at disease onset, or the accumulation of clinical burden over time in affected patients.

Given the inflammatory nature of multiple sclerosis pathological lesions and the positive association of the related *IL-1RN* VNTR with some of the clinical features of multiple sclerosis, these results are somewhat unexpected and contrast with data coming from similar genetic studies in Alzheimer's disease, a degenerative disease of the CNS where the role of inflammatory mechanisms is not as established as in multiple sclerosis.⁴

These data contribute to the debate over the role of inflammation in multiple sclerosis,

especially as recent reports have surprisingly suggested that inflammation may even be protective (rather than having a pathogenic role) in experimental animal models of multiple sclerosis.⁵

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Hyperhomocysteinaemia in Alzheimer's disease and expression of cell cycle markers in the brain

We report that moderately increased concentrations of serum total homocysteine in Alzheimer's disease are associated with the expression of cyclin E (a marker of entry into the cell division cycle) in neurons of the hippocampus. Aberrant entry of neurons into the cell cycle might be an early step in the pathological process.

Expression of proteins related to the control of the cell division cycle has been found in the nuclei of neurons in the cerebral cortex in Alzheimer's disease and it has been proposed that the expression of such proteins, in the absence of cell division, might lead to death of neurons by apoptosis or to the development of neurofibrillary pathology.¹ If the aberrant expression of cell cycle markers is part of the pathological process, then it is important to identify possible factors that might trigger the entry of neurons into the cell cycle. Moderately increased concentrations of plasma total homocysteine, an established risk factor for vascular disease,² are also associated with histopathologically confirmed Alzheimer's disease.³ As in vitro studies have shown that homocysteine can influence the cell cycle in vascular smooth muscle cells and in endothelial cells,⁴ we wondered whether the expres-

Serum total homocysteine concentrations (mean $\mu\text{M/l}$ (SD)) in relation to neuronal expression of cyclin B and cyclin E

	Absent	Present	p Value (ANOVA, Kruskal-Wallis)
Cyclin B	17.1 (8.7)	16.5 (4.5)	0.75
Cyclin E	15.35 (4.2)	18.1 (6.2)	0.045

sion of cell cycle markers in neurons in Alzheimer's disease might be associated with hyperhomocysteinaemia.

We studied the first 60 patients in the Oxford Project to Investigate Memory and Aging (OPTIMA) where both serum homocysteine and postmortem hippocampal tissue were available. Forty eight patients had a histopathological diagnosis of pure Alzheimer's disease, nine had Alzheimer's disease mixed with vascular pathology and three were controls, without CNS pathology. Total serum homocysteine concentrations were determined in blood samples taken at entry of each patient into the study, on average 29.7 (SD 19) months before death.³ The expression of cyclins B and E was studied by immunohistochemical methods⁵ in the nuclei of neurons in the hippocampi by an examiner blind to the diagnosis and to the value of serum homocysteine.

Cyclin B expression in neuronal cell nuclei was found in 50 patients with Alzheimer's disease, and cyclin E expression was detected in 27 patients. The concentration of total serum homocysteine in those patients who expressed cyclin B was no different from that in patients who did not express this cyclin. However, the mean concentration of homocysteine in patients who expressed cyclin E in the brain was 18% higher ($p<0.045$) than that in those who did not express this cyclin (table). Serum vitamin B12 and serum and red blood cell folate concentrations were not significantly different in patients who expressed the cyclins compared with those who did not. To control for the possible influence of other known determinants of serum homocysteine, logistic regression was carried out to see if age, sex, serum creatinine, and serum homocysteine were related to the expression of cyclins B or E. The only significant effect was of homocysteine on expression of cyclin E ($p=0.04$), which was independent of the other factors.

The cell division cycle is a tightly controlled sequence of events that is driven by the sequential nuclear expression and activation of cyclin and cyclin dependent kinase complexes. The nuclear expression of cyclin E is evidence that the neurons have re-entered the cell division cycle whereas expression of cyclin B indicates progression of the cycle to the G2 phase. We suggest that the association of hyperhomocysteinaemia with cyclin E expression, but not with cyclin B expression, may indicate a mitogenic role for homocysteine. The mechanism could be indirect, through the action of homocysteine on the cerebral vasculature, or it might reflect a direct mitogenic action of homocysteine on neurons. Further work is required to test these hypotheses. The rate of atrophy of the hippocampus in Alzheimer's disease is more rapid in patients with increased concentrations of serum homocysteine.³ Thus, if entry into the cell cycle is part of the pathogenic process, then lowering homocysteine concentrations in the blood might slow the progression of the disease.

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CORRESPONDENCE

Visual field defects associated with vigabatrin monotherapy in children

In the December issue of this *Journal* Lawden *et al*¹ found in an adult population receiving vigabatrin (VGB), mostly in association with other antiepileptic drugs, a high prevalence (52%) of visual field defects. These abnormalities were not reversible after discontinuation of VGB therapy.

Since 1990, several authors have reported circumferential narrowing of the visual field with characteristic temporal sparing in patients treated with VGB. Although a visual field defect is the most common cause for discontinuation of VGB therapy, no conclusive data are presently available to explain the pathogenesis of this major side effect.^{1,2} Interestingly, retinal dysfunction has been primarily described in patients receiving VGB in combination with other antiepileptic drugs, whereas only a few cases have been reported in patients treated with VGB as a monotherapy.² Despite increasing attention to this complication, the actual prevalence of visual field defect associated with VGB therapy remains poorly defined. Backstrom *et al* have reported a prevalence of less than 0.10%³ and the Hoechst Marion Roussel Pharmaceutical Company has estimated that the incidence of visual field defect is about 0.15%. Other authors, including Lawden *et al*, however, have recently challenged these data, suggesting a considerably higher prevalence.^{1,2} Such discrepancies can be explained by several factors, including delayed appearance of visual field defects after initiation of VGB treatment (several months up to 7 years), high prevalence of non-symptomatic cases,⁴ and lack of systematic studies. In addition, the often used auto-

mated perimetry (Humphrey field analyser) seems to be significantly less sensitive than the Goldmann kinetic perimetry in detecting visual field defects. These limitations are particularly relevant in assessing the incidence of visual field defects in the paediatric population, given the limited compliance during visual field testing and difficulties of diagnosing visual symptoms in very young children.

We have followed up 13 paediatric patients treated with VGB monotherapy, whom we have systematically screened to detect visual field defects associated with this therapy, even in the absence of visual symptoms. Our patients were aged 5 to 16 years (mean 10.5 (SD 3.8) years) and received VGB monotherapy for localisation related epilepsy during an average period of 41 (SD 18) months (range 8-64 months). In all cases, significant improvement of seizure control was obtained. Routine visual field examinations were not performed until the first reports of visual field defects associated with VGB treatment were published.⁵ Since 1997, systematic kinetic perimetry was performed in all patients and careful attention was paid to identify visual symptoms during regular follow up visits. Clinical evidence of impaired peripheral vision was not apparent in any of our patients. However 8/13 (62%) patients were diagnosed with retinal dysfunction characterised by moderate, concentric narrowing of the visual field with temporal sparing in six patients and severe narrowing of the visual field without temporal sparing in two patients; VGB therapy was discontinued in all patients with visual field defects. Partial recovery after discontinuation of the therapy was not found in any of our patients. By contrast with the above results, no evidence of visual field defects was diagnosed with the Goldmann technique, in 12 control patients with localisation related epilepsy treated with carbamazepine monotherapy.

To our knowledge, these data constitute the largest reported series of VGB monotherapy in the paediatric population. Our results show that, despite severe limitations in diagnosing visual field defects in children, systematic screening can reliably detect visual field anomalies in the paediatric population. Routine screening should be performed even in non-symptomatic children. Similarly to recent reports in the adult population,² our data show that visual field defects are not limited to patients receiving VGB in combination with other antiepileptic drugs but can develop also in children on VGB monotherapy. Our series data in a paediatric population are similar to the data reported by Lawden *et al* in an adult population. They also suggest an overall prevalence of visual field defects considerably higher than previously reported, and show that retinal lesions associated with VGB therapy are not reversible.

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Hedonistic homeostatic dysregulation in patients with Parkinson's disease on dopamine replacement therapies

We read with much interest the article by Giovannoni *et al*¹ depicting the clinical entity that goes under the name of "hedonistic homeostatic dysregulation" in parkinsonian patients.

Obviously, the scientific background that allowed the authors to disentangle the syndrome includes two basic concepts: (1) exogenous dopaminergic stimulation and its fluctuations can and do affect mood in the parkinsonian patient and (2) the target of this influence is the reward related dopamine system, arising from the ventral tegmental area of the mesencephalon and innervating wide regions of the frontal and temporal lobes. Nowadays, these concepts may seem trivial, but they were certainly not so in the late 1980s, when I coauthored two papers that appeared in this *Journal*.^{2,3} Contrary to Giovannoni *et al*,¹ I do think it fair to remind readers of these articles, because they may help the interested reader to understand more of the long story of Parkinson's disease, dopamine, and depression. In the 1986 paper,² we provided the first controlled demonstration that a state of dopaminergic hypoactivity (end of dose deterioration) was significantly ($p < 0.05$) associated with a negative mood swing. The control was represented by patients with advanced rheumatoid arthritis whose motor ability fluctuated predictably because of their joint stiffness on awakening. Patients with Parkinson's disease who were steadily depressed (they were depressed even in their mobile periods), were significantly ($p < 0.05$) less prone to a further mood worsening during immobility than patients who did not have a steady depression. We interpreted this as evidence that the dopaminergic system implicated in mood regulation was so severely affected in the former group, to prevent significant fluctuation. But because the motor status of these patients did fluctuate, the system should have been non-nigrostriatal—that is, mesocorticolimbic. These findings, or their essence, were replicated by independent investigators.⁴ In the second paper,³ we used an amphetamine-like compound—methylphenidate—to test the functionality of the reward or pleasure related dopamine system in patients with Parkinson's disease with major depression, in non-depressed patients with Parkinson's disease, in non-Parkinson's disease patients with major depression, and in age matched healthy controls. The methylphenidate test is used by biological psychiatrists, including studies of people addicted to central stimulants, which relates to the thesis of Giovannoni *et al*.¹ The overall result was that patients with Parkinson's disease with major depression showed characteristically a poor euphoriant response to the intravenous injection of the drug. The

pharmacological target of central stimulants is the mesocorticolimbic dopamine system, and particularly the terminals that synapse in the nucleus accumbens, another concept coming back in the paper by Giovannoni *et al.*¹ Hence we suggested that a derangement of this pathway was very likely to have a contributory role in the pathogenesis of depression. Again there was a replication by at least one independent experimenter.⁵

Now, in the work by Giovannoni *et al.*,¹ this earlier evidence not only is indirectly confirmed, but has gained another, more complex clinical significance. Indeed, the picture that they describe includes, apart from mood disturbances, a series of behavioural abnormalities that are akin to those of addicted people. However, the basic concept remains that, as dopamine is the pleasure transmitter and Parkinson's disease is the dopamine disease, one of the multiple Parkinson's disease facets is a disease of the brain pleasure centres.

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Giovannoni and Lees reply:

Cantello further highlights the involvement of the dopaminergic system in mood and reward. His earlier work demonstrates that this system is dysfunctional or hyporesponsive in patients with Parkinson's disease who are depressed. In comparison patients with Parkinson's disease with hedonistic homeostatic dysregulation have cyclical dysfunction of the dopaminergic reward system, with periods of hypofunction and hyperfunction. It is well known and widely accepted that patients with Parkinson's disease have a cyclical mood disorder, which mirrors the fluctuations in their motor function. What we wanted to highlight in our article is that in a few patients this cyclical mood disorder provides the substrate for the development of a behavioural disorder not too dissimilar from addiction. We deliberately avoided using the term addiction because of its negative connotations and the difficulty of untangling the motor requirements from the mood elevating effects of dopamine replacement therapies.

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BOOK REVIEW

Solitary cysticercus granuloma. The disappearing lesion Edited by: VEDANTAM RAJSHEKHAR and MATHEW J CHANDY. (Pp 169, £9.95). 2000. London: Sangam Books. ISBN 0 86311 815 1.

Cysticercosis (*Taenia solium*) is the commonest parasitic disease of the central nervous

system. The infestation is endemic in several countries in Latin America, Asia, and Africa. Epilepsy is by far the most common clinical manifestation and in endemic areas it is the commonest cause of seizures in adults.

This is an excellent monogram with authors who are very experienced in dealing with cysticercosis. The "disappearing lesions" is a term which was introduced from India and the authors go into the aetiology, clinical manifestations, and medical and surgical treatment as well as antiepileptic drug therapy of patients with a single solitary granuloma. The illustrations are excellent and both CT and MRI are well explained and quite clear.

The book is divided into 13 chapters, all the chapters except one are written by authors from the same institute in India. The lack of detailed immunological background to cysticercosis and the possible biological features that can lead to its chronicity, activation, and eventual destruction is a little disappointing. There is one chapter on immunology but it concentrates on the value or lack thereof of immunological tests in the diagnosis of solitary granulomas due to cysticercosis. The chapter on pathology is much more oriented to histopathology rather than the molecular basis of the disease.

The book would have benefited much from including authors from other institutions world wide. Having said that, this book remains valuable as a monogram on a common and in many cases perplexing clinical presentation.

With modern travel, patients with cysticercosis are seen throughout the world; neurologists and neurosurgeons should be familiar with this condition to avoid unnecessary surgery.

This book is not only valuable for those working in endemic areas but perhaps it is more valuable for those working in non-endemic areas of the world where patients present with single enhancing CT lesions and those treating them have little experience of the disease.

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