

## LETTERS TO THE EDITOR

### Risperidone in levodopa induced dyskinesias

Levodopa induced dyskinesias represent a common complication of the chronic treatment of patients with Parkinson's disease.<sup>1</sup> Refining the schedule of levodopa administration and adding controlled release preparations of levodopa, or dopamine agonists, or both often prove insufficient to control these problems. Pharmacological agents which exert a mild antagonism on striatal dopamine receptors or modulate the dopamine systems by interacting with serotonergic pathways have recently shown beneficial effects in levodopa induced dyskinesias.<sup>2,3</sup>

Risperidone is a new, atypical neuroleptic drug with potent serotonin-5<sub>2</sub> and secondary dopamine-D<sub>2</sub> antagonist properties.<sup>4</sup> It has antipsychotic effects with a low incidence of extrapyramidal side effects, a feature which makes this drug a candidate for the treatment of levodopa induced psychosis and dyskinesia in patients with Parkinson's disease. We have previously obtained beneficial effects with low dosages of risperidone in levodopa induced psychosis in patients with Parkinson's disease.<sup>5</sup> Here we report our open experience with low dosages of risperidone in levodopa induced dyskinesias.

Eight patients (five women, three men) with advanced Parkinson's disease, motor fluctuations, and levodopa induced dyskinesias took part in the study. All gave informed consent. Clinical details were as follows: mean age 67.3 (range 57-81) years; mean Parkinson's disease duration 12.7 (8-20) years; Hoehn-Yahr stage in "off" phase: IV in five patients, III in three patients; mean duration of levodopa therapy 9.6 (range 6-14) years; duration of levodopa induced dyskinesias 4.3 (range 2-7) years. All but one had peak dose dyskinesias. The remaining patient had diphasic (beginning and end of dose) dyskinesias. The risperidone dosages ranged from 0.125 to 0.25 mg once a day, at bedtime. The chronic antiparkinsonian treatment (levodopa/dopa decarboxylase inhibitors monotherapy in four patients; levodopa plus bromocriptine or pergolide in four patients) remained unchanged during the trial. The severity of parkinsonism and dyskinesias was assessed at regular intervals during the trial using the unified Parkinson's disease rating scale (UPDRS; part III-motor scale)

and the abnormal involuntary movement scale (AIMS). All patients but one were evaluated during the period of maximum benefit from therapy ("best on" condition); the remaining patient, with diphasic dyskinesias, was evaluated during the beginning of the levodopa effects. Patients were asked to fill in diaries at home with the number of hours spent in "on" and "off" conditions, but data were available only in a few cases and were not reported.

The table summarises the results. After risperidone therapy all the patients had moderate to pronounced reduction in dyskinesias. These effects have been maintained during the follow up (mean 11 (range 6-21) months). The final AIMS score of the group was significantly lower compared to the baseline score (P<0.01, Wilcoxon test). Three patients (2, 4, 6) took 0.25 mg risperidone/day with no modification of their parkinsonism. Three other patients (1, 3, 5) were unable to tolerate the initial 0.25 mg dosage owing to a worsening of parkinsonism (increase of number of hours spent in "off" conditions or worsening of "on" conditions) and their dosage was therefore reduced to 0.125 mg/day after some weeks. This produced a smaller improvement in the dyskinesias with no great worsening of parkinsonism (table). One patient (7) received 0.125 mg risperidone/day from the beginning of the trial. The last patient (8), with diphasic dyskinesias, received 0.25 mg risperidone/day for about one year, with considerable improvement in the dyskinesias. Subsequently, owing to a worsening of parkinsonism, the risperidone dosage of this patient was reduced to 0.25 mg twice a week, although some improvement in dyskinesias was maintained. The final UPDRS score of the group showed no significant changes when compared with the baseline score (Wilcoxon test) (table). No serious side effects were encountered during this risperidone trial.

The results of this open experience suggest that in some patients with Parkinson's disease low dosages of risperidone might have beneficial effects on levodopa induced dyskinesias, without causing significant worsening of parkinsonism. In the light of the pharmacological properties of risperidone, both dopamine and serotonin antagonism might play a part in the effects we found on levodopa induced dyskinesias. It has to be stressed that, owing to the extreme sensitivity of patients with Parkinson's disease to both the beneficial and undesirable effects of neuroleptic drugs, treatment with risperidone must be started with very low dosages (0.125 mg daily) and continued with caution. In conclusion, these results warrant larger, controlled studies to

test the therapeutic potential of risperidone in levodopa induced dyskinesias.

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### Lack of association of a Taq 1 polymorphism of the human myelin oligodendrocyte glycoprotein gene with multiple sclerosis in a population of patients from the Southampton area

The lesions of multiple sclerosis are most often held to be caused by an immune attack on CNS myelin.<sup>1</sup> The nature of the antigens involved remains obscure, but peptides from at least two major myelin proteins—myelin basic protein and proteolipid protein—are known to cause cell mediated demyelination in animals (experimental allergic encephalomyelitis) which in some ways resembles human multiple sclerosis.<sup>1</sup> Minor myelin components may presumably also act as autoantigens. Myelin oligodendrocyte glycoprotein (MOG) is a quantitatively minor myelin protein localised to oligodendrocyte cell bodies and processes and to the outer layer of CNS myelin sheaths. Originally detected by a mouse monoclonal antibody to rat cerebellar glycoproteins, the amino acid sequence of MOG has been deduced from cDNAs of rat, mouse, human, and bovine species and shows a high degree of evolutionary conservation and sequence motifs identifying it as a member of the immunoglobulin superfamily. In common with several other members of this family, MOG has a membrane spanning domain and an extracellular glycosylated N-terminus and its presence on the outermost surface of myelin and the oligodendrocyte plasma membrane may make MOG accessible to the immune system. The evidence that MOG may act as an autoantigen in multiple sclerosis includes reports that anti-MOG antibodies cause extensive CNS demyelination both in vivo and in vitro, that peptides from the primary sequence of MOG can produce experimental allergic encephalomyelitis, that the predominant T cell response in a population of patients with multiple sclerosis is to MOG and that antibodies to MOG can be demonstrated in the CSF and serum of patients with multiple sclerosis. Additionally the human MOG gene has been localised to a region of the major histocompatibility complex on chromosome 6, the significance of this in immune theories of the causation of multiple sclerosis being unclear.<sup>2</sup> Against this

Patient No	Levodopa dosage (mg/day)	Risperidone dosage (mg/day)	Duration*	UPDRS score		AIMS score	
				Baseline	Final	Baseline	Final
1	1450	0.125	12	48	48	14	6
2	1100	0.25	21	23	23	18	2
3	500	0.125	9	14	14	16	1
4	800	0.25	12	32	32	9	5
5	1025	0.125	7	6	13	16	9
6	875	0.25	9	22	25	26	12
7	925	0.125	6	44	44	22	14
8	675	0.25	12	23	29	12	5
Mean	919	0.187	11	26.5	28.5	16.6	6.75
SD	287	0.067	4.66	14.2	12.7	5.4	4.6
p Value†				NS		<0.01	

\* Months of duration of risperidone treatment.

† Comparison of final v baseline scores (Wilcoxon test).

**Table 1** Distribution of *Taq 1* digest polymorphic bands in patients with multiple sclerosis and controls

Band size (kb)	n (%) showing polymorphic bands	
	Patients (n = 40)	Matched controls (n = 80)
4.9	11 (27.5)	23 (28.8)
4.4	39 (97.5)	78 (97.5)
3.25	38 (95)	76 (95)
2.4	14 (35)	32 (40)
1.9	5 (12.5)	7 (8.8)
1.65	15 (37.5)	27 (33.8)

background, analysis of the human MOG gene has defined its intron/exon structure and provided evidence that a 1.9 kb *Taq 1* restriction fragment length polymorphism (RFLP) of the human MOG gene could be linked to multiple sclerosis in a significant fashion in a population of Australian patients with multiple sclerosis.<sup>3</sup> We have examined this *Taq 1* polymorphism in a population of patients with multiple sclerosis and controls from the Southampton area.

Venous blood samples were obtained from 40 patients with multiple sclerosis in the Southampton area and from 80 age and sex matched controls. The patients were 29 women and 11 men diagnosed as having clinically definite multiple sclerosis by the Poser criteria.<sup>4</sup> The age range was 23–43 years with a mean of 33.9 years. DNA was extracted by standard procedures,<sup>5</sup> digested with *Taq 1*, electrophoresed, and subjected to Southern blotting using the same human MOG cDNA as previously.<sup>3</sup> Six polymorphic bands of 4.9, 4.4, 3.25, 2.4, 1.9, and 1.65 kb were found, plus three invariant bands of 1.75, 1.25, and 1.05 kb. This contrasts with the Australian study, in which *Taq 1* digestion of human genomic DNA and hybridisation with the same MOG cDNA probe showed five polymorphic bands of 5.25, 4.65, 2.4, 1.9, and 1.05 kb and only one invariant band of 1.7 kb. In that study the 1.9 kb band was present in 12.2% of patients with multiple sclerosis and 3.7% of controls, a difference which was significant ( $p < 0.05$ ). The table shows the distribution of the *Taq 1* digest polymorphic bands between patients with multiple sclerosis and controls in the present study; none of these distribution differences were statistically significant. We assume that the 1.9 kb band found here is the same as in the previous study, in which case the incidence in the two sets of patients with multiple sclerosis is very similar—12.5% and 12.2%. However the incidence of this RFLP in the control group in the present study was much higher than in the previous study—8.8% *v* 3.7%—thus denying significance. We assume our finding of extra invariant bands in *Taq 1* digests of the human MOG gene and largely different sized RFLPs are due to genetic differences in the two populations. This illustrates the difficulties of extrapolating between two geographically widely separated cohorts. It is also important to have comparable groups in terms of clinical types of multiple sclerosis, age and sex structures, and nature of the control populations used.

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### Pneumocephalus as a complication of metastases and eroding infection in the sacral region

Pneumocephalus is a well known and rare disease that denotes a pathological presence of intracranial air. Below, we describe an extremely rare case of the development of pneumocephalus.

A 66 year old woman was admitted to our clinic with headache persisting for the previous two months. The headache had become particularly severe and had been accompanied by vomiting during the previous week. One year before being admitted to our clinic, the patient had undergone brain CT along with other tests and the results were normal. Medical records indicated that 10 years ago the patient had undergone surgical treatment of an adenocarcinoma of the rectum. Since then she had been under an oncologist's observation. Seven years after surgery, metastases developed in the L5

vertebral body and the sacrum. This was confirmed by radiography of the lumbosacral spine and the sacrum, by radioisotope bone scans, by sacrum CT, and by pathohistological analysis of the biopsy of the sacral region. Despite implemented radiation therapy the general condition of the patient deteriorated. She lost weight and finally became paralysed. Skin and subcutaneous tissue defects appeared in the sacral region and did not heal. Repeated cultures isolated *Enterococcus*, *Enterobacter* species, and *Hafnia alvei*. The patient refused the proposed necrotomy; instead she received antibiotic treatment. At admission the patient was extremely thin, subfebrile 37°C; cardiocirculatory and respiratory systems were stable. Findings of the anus praeter naturalis in the abdominal region were normal. In the sacral region a deep seated ulcerative lesion 12×9 cm in size was visible, covered by brown strata, which secreted purulent and bloody substance. A neurological examination indicated that the patient was conscious, that her speech was normal, and that there were no signs of meningeal irritation. Flaccid paraplegia was present together with sensory modalities impaired in the right L4 and S1 dermatome and the left L5, S1, S2, and S3 dermatome and she was incontinent for faeces and urine. Routine laboratory blood tests showed the following increases: erythrocyte sedimentation rate 56 mm/h, ALP 105 U/l, ALT 59 U/l, AST 28 U/l and reduced values of HGB 113, HCT 0.345, MCHC 26.4 g/l. The findings from other laboratory tests were normal. The fundus oculi examination was normal. Findings from radiography of the paranasal sinuses and the skull were normal except for the presence of air in the third and in the lateral ventricles. The brain CT indicated that the size of the ventricular system was normal and the ventricular system was for the most part filled with very hypodense zones which, according to absorptivity, corresponded to the air. Some air was visible around the brainstem. Such a finding indicates a pneumocephalus (fig 1). The sacrum CT showed a large skin and subcutaneous defect. The sacrum was mostly destroyed and filled with

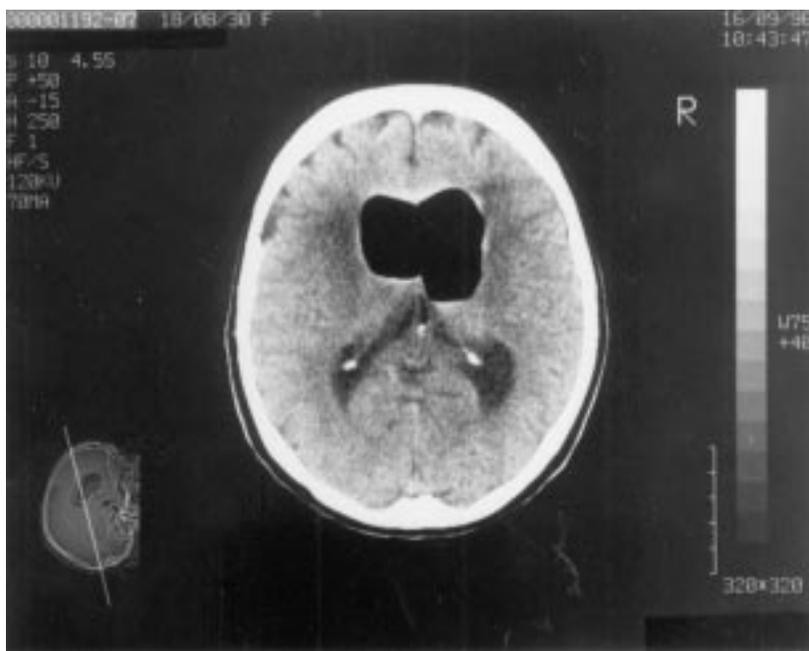


Figure 1 Brain CT showing intraventricular air.

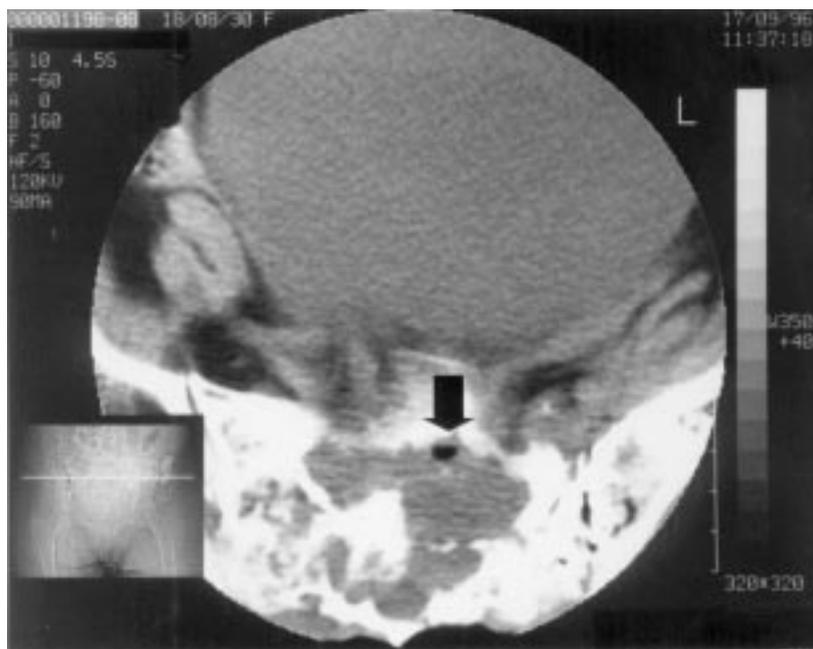


Figure 2 CT of the sacrum. The arrow points to a small hypodense area representing air.

zones corresponding to soft mass density. Sporadically, inside the spinal canal some small hypodense zones were visible, the absorptivity of which corresponded to air (fig 2). Abdominal and pelvic CT scans were normal. Findings of lung and heart radiography and ECG were normal. The EEG indicated slow activity. Lumbar puncture was not carried out. Because of the condition of the patient neurosurgical intervention did not take place. The patient's condition gradually deteriorated and she died three days after admission to hospital. The basic pathophysiological mechanism of pneumocephalus is the development of a dural fistula which permits the flowing out of the CSF and the entry of air into the subarachnoid space, which, because it cannot flow back, successively accumulates intracranially. In head injuries, pneumocephalus is recorded in 0.5% to 1.0% of all cases.<sup>1</sup> It may also develop as a complication of neurosurgical treatment of chronic subdural haematoma or after posterior cranial fossa surgery.<sup>2</sup> It is described in the craniofacial approach to tumour removal from the base of the anterior cranial fossa as well as in nasal and otological surgery.<sup>3</sup> Intracranial air appears as the consequence of eroding otological infections, of eroding tumours of the brain, nose, and nasopharynx in combination with radiotherapy.<sup>4</sup> It is mostly described as a complication which follows insertion of a nasogastric tube and a case has been described also after insertion of a nasopharyngeal tube.<sup>5</sup> Subarachnoid-pleural fistula and intracranial air may occur after severe chest trauma. Cases after thoracotomy and surgery of the tumour of the lung apex have also been described.<sup>6</sup> Pneumocephalus may also develop when administering epidural anaesthesia and in continuous external lumbar subarachnoid drainage in the treatment of dural fistula.<sup>7</sup> The first symptom of pneumocephalus is a headache which in anterior cranial fossa fractures or eroding processes may also be accompanied by rhinorrhoea. Should the headache intensify and be coupled with other signs of increased intracranial pressure, an urgent brain CT is required to diagnose pneumocephalus. In

most cases it is a small quantity of air and the developed fistula may heal spontaneously. Should the fistula persist, urgent operative repair is needed to prevent brain herniation and death.

We consider the case described above to be exceptionally rare given the way pneumocephalus develops. In our opinion, the destruction of the sacrum, of skin, and of subcutaneous tissue of the sacral region, assigned to a malignant process which was hastened by eroding infection, caused a communication between the subarachnoid space and the surface of the skin. We think that the developed sacrodural fistula is the only possible explanation for the development of pneumocephalus.

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## Paraneoplastic opsoclonus associated with papillary renal cell carcinoma

Opsoclonus is an ocular dyskinesia consisting of involuntary, repetitive, rapid conjugate ocular saccades that are irregular in amplitude and frequency and occur in all directions without an intersaccadic interval.<sup>1</sup> Opsoclonus appears more commonly in children,<sup>2</sup> and in half of such cases in association with neuroblastoma.<sup>1</sup> In adults, the most frequent causes are idiopathic (50%) and paraneoplastic (20%).<sup>1</sup> Among the second group, different types of tumours involving a wide variety of organs have been reported, although no case of renal tumour has been published.<sup>1</sup>

A previously healthy 64 year old man complained of progressive vertigo and unsteady gait, together with mild headache, since a month before admission. At examination he showed severe opsoclonus (increased by saccadic movements and visual fixation), slight cephalic myoclonic movements, and he could not stand or walk because of truncal ataxia. The rest of the neurological evaluation was unremarkable.

Blood tests included white cell count, haemoglobin, erythrocyte sedimentation rate, glucose, urea, creatinine, bilirubin, immunoglobulins, and angiotensin converting enzyme. These were all normal. Serological tests for syphilis and HIV were negative, as was the screening for several tumour markers. Anti-Hu and anti-Ri serum antineuronal antibodies were not detected. On admission, CSF contained 19 mononuclear white blood cells (WBC)/mm<sup>3</sup>, 73 mg/dl protein, with normal glucose concentration and negative cytological examination. Two months later, a new CSF examination showed 40 mononuclear WBC/mm<sup>3</sup>, 47 mg/dl protein, and normal glucose concentration. Serological tests, as well as bacterial and fungal cultures, were negative in both CSF studies. Brain MRI and thoracoabdominal CT were normal.

Soon after the beginning of treatment with 60 mg/day oral prednisone the patient's neurological symptoms gradually improved. Seven weeks later, despite a slow decrease in the dose of prednisone, the patient became asymptomatic. Six months later, he complained of lumbar pain and radiography suggested the existence of lumbar osteoblastic lesions. Both ultrasound and CT studies disclosed a mass in the right kidney, without evidence of any bone metastasis. After a radical nephrectomy, the pathological study gave the diagnosis of a papillary type of renal cell carcinoma. At present, three years after the initial presentation, the patient remains asymptomatic and without any treatment.

Paraneoplastic opsoclonus usually antedates the detection of the underlying neoplasm by a period that may last up to one year.<sup>1,3</sup> This sequence of events was also found in our patient, as the first abdominal CT examination did not detect the tumour. This could be explained by the fact that a substantial proportion of small renal masses can be missed by CT and ultrasound studies.<sup>4</sup> Therefore, we consider that the development of opsoclonus in our patient was probably linked to his renal tumour. The pathogenesis of paraneoplastic opsoclonus is unknown, although there is increasing evidence that it may be immune mediated.<sup>1</sup> It has been proposed that antigenic substances may be shared between certain tumours and portions of the nervous system.<sup>5</sup> This would elicit an efficient immune response against the

tumour, but also against the neural tissue.<sup>5</sup> This hypothesis would be supported by the complete recovery of our patient during treatment with prednisone and before surgery. However, the possibility of spontaneous remission in paraneoplastic opsoclonus cast doubts on the role of steroids on this improvement.<sup>3</sup> In any case, if the mechanism is autoimmune, it would have been mediated by an unknown antineuronal antibody as those known at present were not found in the serum of our patient.

The diagnosis of opsoclonus has to be followed by an extensive search for malignancy which, after the present case, should include renal carcinomas.

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#### In vivo visualisation of the longitudinal callosal fascicle (Probst's bundle) and other abnormalities in an acallosal brain

A 45 year old office clerk with a two year history of intermittent tension like headache presented with difficulties of walking heel to toe and of exchanging sensorimotor information between both hemispheres (alternating bilateral tapping, contralateral mirroring of finger position, cross localisation of tactile stimuli, finger sequence repetition, and bilateral coordinated arm rotations). There were no complaints about limitations in activities of daily life. The family history was unremarkable regarding motor disabilities, mental retardation, or epilepsy. MRI (A, C-F: TR 25 ms, TE 6.9 ms; B: TR 4000 ms, TE 90 ms) disclosed an absence of the corpus callosum, massa intermedia, posterior commissure (figure A) and septum pellucidum (figure C-F) and a hypoplastic anterior commissure (figure A). On the basis of the history and the anatomic findings, the patient can be classified as having an "asymptomatic" acallosal brain or a complete agenesis of the corpus callosum.<sup>1</sup>

The convolutional pattern on the medial surface of the hemisphere was abnormal with gyri radiating in a fan-like fashion and without a visible callosomarginal sulcus (figure A). On the axial and coronal slices an anteroposteriorly running fibre tract (arrow head, figure B-F) was visible which could clearly be distinguished from the medially situated cingulate gyrus (arrow in figure D). This fibre tract has been named after Probst (Balkenlängsbündel of Probst, callosal longitudinal bundle) who saw it as a typical sign of agenesis of the corpus callosum.<sup>2</sup> Pathoanatomical investigations of the origin and course of the fibre tract led to the conclusion

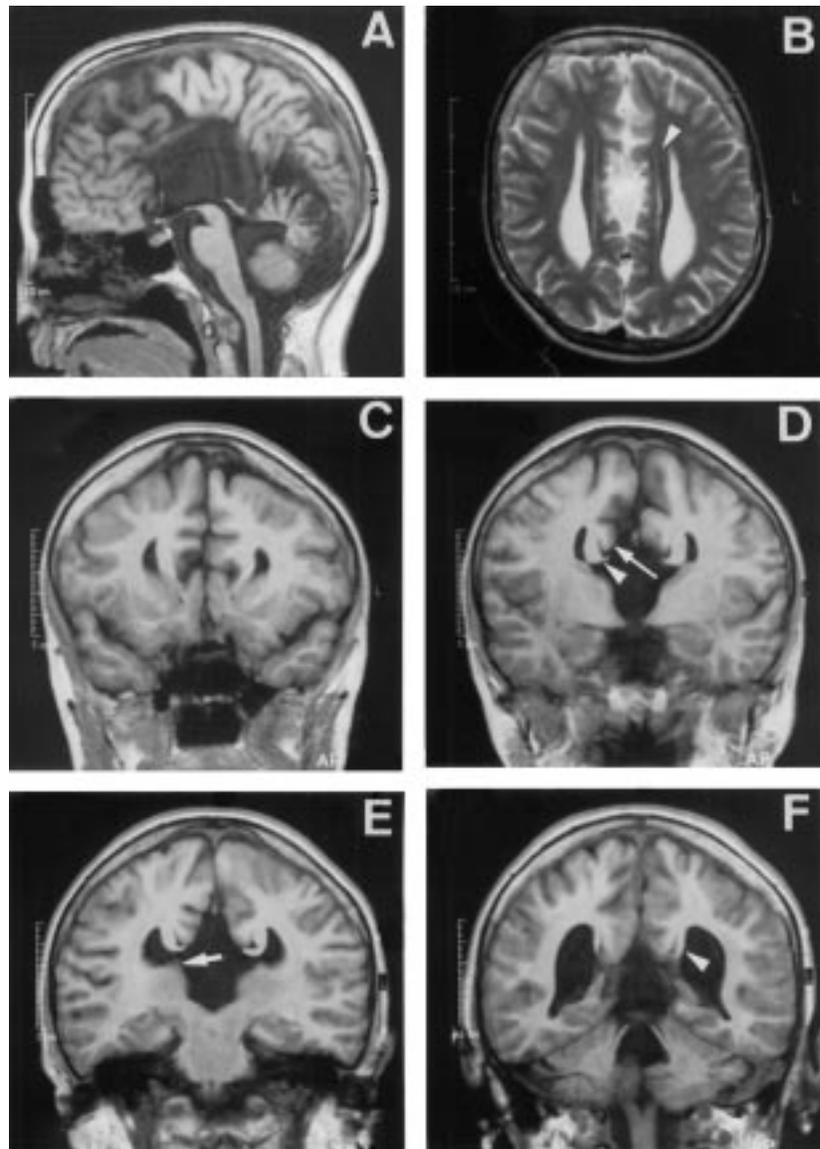
that it consists of heterotopic myelinated callosal fibres and results from a migration disorder of callosal fibres.<sup>2,3</sup> During embryogenesis the fibres are thought to arrive at the midplane where they are hindered in their further migration across the midline and then change their direction of growth into an anteroposterior direction and by this form the Probst's bundles in each hemisphere.<sup>3</sup> This hypothesis about the development of the Probst's bundles is supported by recent investigations in acallosal mice.<sup>4</sup>

The absence of the corpus callosum and the volume of the Probst's bundles influence the shape of the ventricles. The posterotemporal parts of the lateral ventricles and the third and fourth ventricle are enlarged. Frontally, the Probst's bundles are thickest and become smaller on their frontooccipital course (figure B). Frontally they are comma shaped, bulge into the medial wall of the lateral ventricles, and cause a narrowing and dorsolateral transposition of them (bull horn formation of the ventricles in figure D, E).<sup>2,3</sup> Posteriorly, the Probst's bundle forms a thin layer on the upper medial wall of the lateral ventricles which are consecutively dilated

(figure F). Additionally, a completely separated fornix could vaguely be identified at the lower medial wall of the lateral ventricles directly ventral to the longitudinal callosal bundle (figure D, short arrow in E).

This case illustrates that MRI allows a precise in vivo examination of the anatomical situation in patients with accidentally detected acallosal brains. Especially, the detailed characteristics of Probst's bundle were to our knowledge previously only defined pathoanatomically, which is somewhat limited by shrinkage artifacts. The detection of Probst's bundle during life might be useful to further elucidate the function of this fibre tract by evoked potential studies using transcranial magnetic or electric brain stimulation similar to the approach described for an activation of interhemispheric fibres in humans.<sup>5</sup>

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In vivo visualisation of the longitudinal callosal fascicle (Probst's bundle) (arrow head) and other abnormalities in an acallosal brain. Long arrow in D=cingulate gyrus; short arrow in E=fornix.

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### Self induced noogenic seizures in a photosensitive patient

Self induced seizures are commonly encountered in photosensitive epileptic patients.<sup>1</sup> Pattern,<sup>1</sup> musicogenic, and cheirogenic<sup>2</sup> self induced seizures are rarely described. In all cases the manoeuvres employed by the patients implicate external stimuli. Self induced seizures with internal stimuli have not been reported.

In noogenic or thinking epilepsy seizures are precipitated by elaborate mental activity implicating decision complexity, sequential factors, and possibly related stress. In this condition a third of the patients also show photoparoxysmal discharges but not clinical photosensitivity.<sup>3</sup>

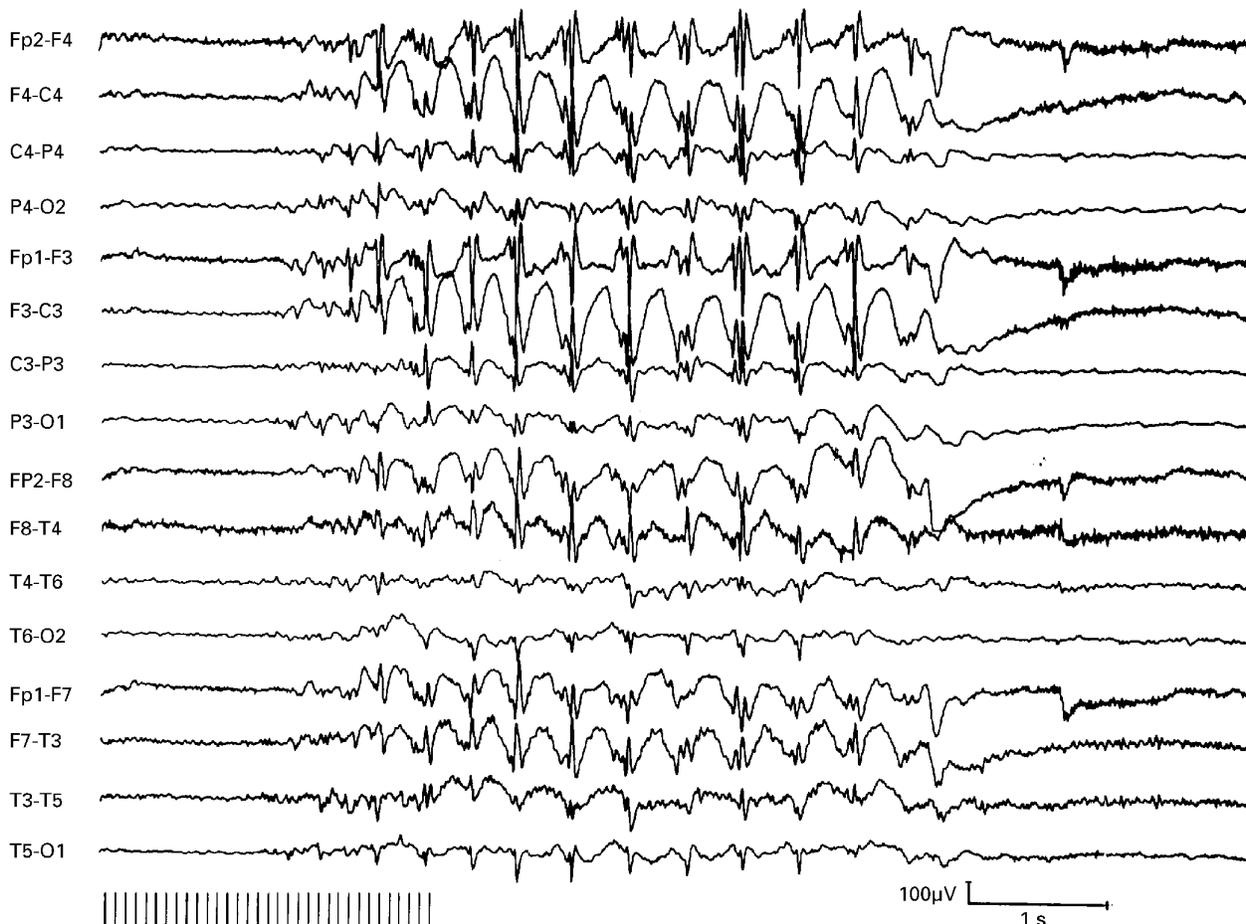
We report a photosensitive patient who induced absences by a specific noogenic process of predominant emotional character.

A 20 year old man of normal intelligence had a family history of seizures and a febrile convulsion at the age of 4. At the age of 11 he had generalised tonic-clonic seizures on three occasions while watching television. At that stage EEG showed frequent spontaneous generalised 3–4 Hz polyspike and wave discharges of up to five seconds and pronounced photosensitivity to frequencies from 10 to 50 Hz. Physical means for seizure prevention such as dispersion screens fitted on the TV screen, polaroid glasses, and monocular viewing had limited success. One year later, treatment with sodium valproate was initiated because of additional spontaneous clusters of absence seizures often followed by generalised tonic-clonic seizures. Absences consisted of brief repetitive episodes of “stopping his activities and looking vacant”. They would occur any time of the day but often in the morning after awakening. He could be taken out of this state by his mother shouting his name but if this was unsuccessful, absences would progress to generalised convulsions. This period coincided with the death of his father.

Seizures continued despite increasing sodium valproate to 2000 mg daily but poor compliance was confirmed on serial estimations of drug blood concentrations. Self induction was suspected but this was categorically denied by the patient and there was no evidence of recognisable relevant manoeuvres

such as eyelid blinking, hand waving, or hyperventilation. Television, flickering lights, excitement, enjoyment, and concentration on previous emotional experiences were among the precipitating factors he listed on questioning at the age of 15. A video-EEG showed brief generalised polyspike and wave discharges only during intermittent photic stimulation (figure). There were no spontaneous or hyperventilation induced discharges. Neurological examination and brain MRI were normal.

Absences were dramatically reduced at the age of 18 when 50 mg lamotrigine given at night was added to sodium valproate, and ceased completely eight months later when the patient changed his lifestyle by starting university studies and limited self employment. One year later, he retrospectively admitted self induction by “concentrating on upsetting things in the school” and thinking of his father. “I know when I self induced the seizures. I could self induce the fits quite easily, if I thought about my father. Like the time I spent with him, also the time that he was in the hospital or things like that. This could induce the fits. I never did it to gain anything, I did it to get away from other people”. He also explained that he did not use light stimulation for self induction “because that would become obvious to others and betray my habit”. He employed self induction mainly at school and with the purpose of inducing absences. A new video-EEG at the age of 18 years showed only minor posterior



A typical absence seizure induced by 25 Hz intermittent photic stimulation at the age of 15. The patient is unresponsive and stares.

photoparoxysmal responses and failed to induce abnormalities on thinking about his father.

Presently, the patient has only occasional generalised tonic-clonic seizures associated with alcohol excess or sleep deprivation. He also has a skin rash diagnosed as Darier's disease.

This patient with typical absences, generalised tonic-clonic seizures, and clinical photosensitivity, presents two interesting features regarding his reflex seizures. Firstly, both flickering lights and complex internal noogenic stimuli were specific modes of seizure precipitation. Secondly, he self induced seizures by an emotional noogenic process and not by the common method of manipulating light stimulation. Like most of the patients with self induced seizures he concealed his habit for many years. Wilful confession was the only way to disclose it as no external stimuli were involved. Absences and self induction ceased due to conscious effort and appropriate medication.

Specific modes of precipitation in reflex epilepsies are simple and complex. Simple stimuli such as flickering lights are usually external, have a short time response, and are easy to identify.<sup>1</sup> Conversely, complex stimuli as in noogenic epilepsy are internal, have a longer time response, and are not discernible to the observer.<sup>3</sup> The electroclinical characteristics of the generated response do not seem to be primarily determined by the type of the stimulus (simple or complex) and may be focal or generalised. In photosensitive epilepsy clinical seizures and EEG discharges may be restricted to the occipital regions or generalised<sup>1</sup> and the underlying mechanisms seem to involve a non-uniform hyperexcitability of the occipital cortex and a critical mass of neuronal excitation and synchronisation. Similarly, seizures precipitated by higher cognitive processes such as thinking may be generated by hyperexcitable neurons in the relevant cortical areas—namely, the parietal lobes, are generalised, and the EEG phenomenology may vary.<sup>3</sup> That in noogenic reflex seizures cortical hyperexcitability may expand to the occipital regions is implied by the fact that a third of the patients also show photoparoxysmal responses to intermittent photic stimulation.<sup>3</sup> The thought process that is linked with seizure precipitation does not seem to be uniform. Spatial processing,<sup>3</sup> strategic or consequential thinking,<sup>4</sup> and even prominently emotional processes have been proposed as decisively activating factors. In our patient the effective triggering stimuli are photic and complicated, primary emotional thinking processes. He elected the more elaborate noogenic trigger for self induction although photic manoeuvres would possibly be more provocative. This may suggest that the experience of the seizure itself was not the main objective as we previously suggested for another photosensitive patient who used patterns but never light for self induced seizures.<sup>5</sup>

A practical aspect of this report is that self induced noogenic seizures are difficult to discover, may escape detection for many years, and may not be as unique as this case may indicate.

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#### A necropsied case of Machado-Joseph disease with a hyperintense signal of transverse pontine fibres on long TR sequences of magnetic resonance images

Machado-Joseph disease refers to autosomal dominant spinocerebellar degeneration, and the gene responsible for the disease exhibits an expanded trinucleotide CAG repeat in chromosome 14q32.1.<sup>1</sup> Machado-Joseph disease has a wide range of clinical manifestations in addition to the cerebellar ataxia. The diverse disorders are characterised neuropathologically by the involvement of the pallidolulysian, dentatorubral, pontocerebellar, cochleocerebellar, and spinocerebellar systems, lower motor neurons, and dorsal root ganglia. Previous MRI studies disclosed only mild cerebellar and brain stem atrophy in Machado-Joseph disease.<sup>2</sup> Our MRI examinations in 31 cases disclosed atrophy of the pons, middle, and superior cerebellar peduncles, and frontal and temporal lobes, together with fourth ventricular dilatation.<sup>3</sup> A third of the cases displayed a hyperintense signal of the transverse pontine fibres, which had been found previously in patients with olivopontocerebellar atrophy.<sup>4</sup> Here, we report on a patient with Machado-Joseph disease with an abnormal pontine signal on MRI, nine months before death, and pathological findings of the necropsied brain.

A 46 year old man had been in good health until the age of 23 when he began to stagger and slur his speech. He showed progressive difficulty in walking and was bedridden at the age of 37. Eight years later, he was admitted to hospital because of dysphagia and dysarthria. His father had had Machado-Joseph disease and died at the age of 40.

The patient was 160 cm tall and weighed 34.8 kg. He was mentally inactive, but his orientation and memory seemed normal. Communication was difficult due to cerebellar ataxia, dystonia, and severe hypophonia. Abduction of the eyes was limited bilaterally, with impaired upward gaze, slow saccades, and gaze evoked horizontal nystagmus. He had bulging eyes and his speech was very hypophonic. Fine twitching movements were noted in his facial muscles. His limbs were hypotonic and wasted. Muscle strength was weak, and the legs were severely deformed due to contracture. Tendon reflexes in the upper limbs were exaggerated, but knee and

ankle jerks were decreased. The Babinski reflex was positive. Dysmetria and dysidiadochokinesis were present in both arms. Dys-tonic posture was striking in his hands. CAG repeat lengths of the MJD1 gene were 77 and 19 (method described previously<sup>5</sup>). He died of acute interstitial pneumonia at the age of 46, nine months after MRI.

Brain MRI was carried out using Signa Advantage 1.5T. T1 weighted images (TR=450 ms, TE=19 ms), T2 weighted images (TR=3000 ms, TE=102 ms), and the first echo of long TR sequence images (TR=3000 s, TE=17 ms) were taken in the transaxial, coronal, and sagittal planes, at 5 mm thickness with a 2.5 mm gap. Brain MRI disclosed severe atrophy of the anterior lobe of the cerebellum, upper cerebellar peduncles or brain stem, and moderate atrophy of both middle cerebellar peduncles, bilateral frontal (figure A) or temporal cortex, as well as a hyperintense signal in transverse pontine fibres (figure B) and pontine midline on the first echo of the long TR sequence. The hyperintense signal in the pons was narrower and less intense than in most cases of olivopontocerebellar atrophy.

The weight of the fresh brain was 1320 g. Paraffin sections (7 µm) were made after fixing the specimens with formalin and staining with haematoxylin and eosin, Klüver-Barrera, Bodian, and methenamine silver stains, and immunohistochemistry with anti-gliab fibrillary acidic protein and antiubiquitin antibodies. The brain atrophy was moderate in the frontal (figure C) and temporal lobes, and considerable in the pontine base and cerebellum. On microscopical examination, the cell architecture in the cerebral cortex was normal without senile plaques, neurofibrillary tangles, or inclusion bodies. The frontal white matter displayed pallor of the myelin (figure D). The globus pallidus showed mild neuronal cell loss and gliosis. The pontine nuclei, transverse fibres, and upper and middle cerebellar peduncles showed considerable atrophy associated with nerve cell loss, but without gliosis, demyelination, or change in neuronal density (figure E). The cerebellar white matter exhibited slight pallor on Klüver-Barrera staining, and the dentate nuclei showed cell loss and gliosis. The cerebellar cortex was normal.

Characteristic findings on MRI in this case were the abnormal hyperintense signal of transverse pontine fibres and the mild frontal and temporal atrophy. The hyperintense signal in the pons of cases of olivopontocerebellar atrophy has been reported to reflect gliosis and myelin sheath loss along degenerated pontocerebellar fibres.<sup>4</sup> Our previous MRI examinations have disclosed the abnormal signal of transverse pontine fibres in some cases of Machado-Joseph disease, whereas all cases of olivopontocerebellar atrophy show a more hyperintense and wider signal of transverse pontine fibres.<sup>3</sup> The difference might arise from the lack of demyelination and gliosis in Machado-Joseph disease, and the decrease in the volume without change of the neuronal density in the pontine nuclei and transverse pontine fibres in this case.

The frontal atrophy found by MRI in 31 cases of Machado-Joseph disease was examined and found to be more accelerated than in age matched control subjects. The cell architecture of the frontal cortex was well preserved, but pallor of the myelin was noted in the frontal white matter. The frontal atrophy might be produced by demyelination in

the deep white matter. The patient was mentally inactive, but his orientation and memory were not impaired, although a mental test was impossible because of his severe ataxia, dystonia, and hypophonia. Patients with Machado-Joseph disease do not usually show impaired cognitive function, despite mild to moderate frontal or temporal atrophy. A previous pathological study of Machado-Joseph disease disclosed similar frontal atrophy,<sup>6</sup> in which the cerebral cortex was not greatly affected, but the frontal white matter volume was decreased.

In conclusion, the frontal atrophy commonly seen in Machado-Joseph disease may be caused by demyelination in the deep white matter and the hyperintense signal of transverse pontine fibres, visible on long TR sequences of MRI, is presumably due to the characteristic atrophy of the pons in Machado-Joseph disease.

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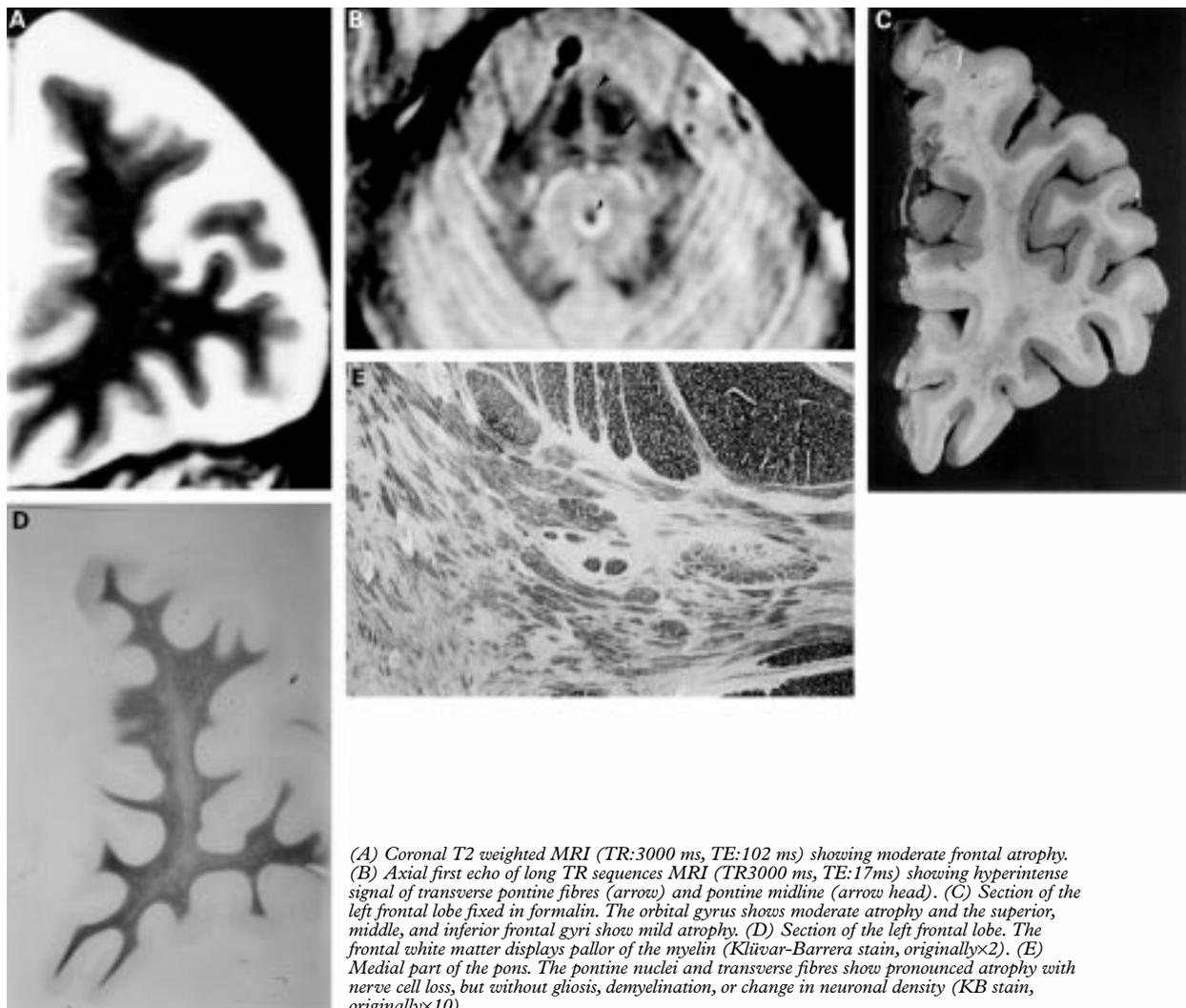
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## BOOK REVIEWS

**Magnetic Resonance in Multiple Sclerosis.** Edited by D H MILLER, J KESSELRING, W I MCDONALD, D W PATY, AND A J THOMPSON. (Pp 200; £50.00). Published by Cambridge University Press, Cambridge, 1997. ISBN0-52 1-47325-X.

This book comprises 171 editorial pages divided into three chapters. It seems more directed towards clinical neurologists rather than neuroradiologists or basic scientists, as its summary suggests, since it is largely concise and simplistic in its explanation of terminology and technology. It attempts to comprehensively consider both the benefits and limitations of MR in multiple sclerosis and its role in clinical practice and is largely successful in its aims. It has an impressive list of authors who undoubtedly represent some of the most senior researchers in the field who have assessed the impact of MR on the management of multiple sclerosis and the insights into pathogenesis it has provided as well as more predictable subjects such as the distribution and morphology of lesions in the disease



(A) Coronal T2 weighted MRI (TR:3000 ms, TE:102 ms) showing moderate frontal atrophy. (B) Axial first echo of long TR sequences MRI (TR3000 ms, TE:17ms) showing hyperintense signal of transverse pontine fibres (arrow) and pontine midline (arrow head). (C) Section of the left frontal lobe fixed in formalin. The orbital gyrus shows moderate atrophy and the superior, middle, and inferior frontal gyri show mild atrophy. (D) Section of the frontal white matter displays pallor of the myelin (Klüver-Barrera stain, originally $\times 2$ ). (E) Medial part of the pons. The pontine nuclei and transverse fibres show pronounced atrophy with nerve cell loss, but without gliosis, demyelination, or change in neuronal density (KB stain, originally $\times 10$ ).

and differential diagnosis. I found one of the most useful sections was the explanation of terms which tend to bring uninitiated neurologists such as myself into a cold sweat such as FLAIR, FSE, ADC, and TE, which are explained in a brief and uncomplicated manner. In addition the review of the role of MR in the ever increasing number of clinical trials which place so much emphasis on this technique as a surrogate marker of disease activity was illuminating. This book is well written and beautifully illustrated, as one would expect, but my only question mark would be the place of this text in the library of a general neurologist. The competition is great and the number of textbooks which consider not only MR but the entire clinical picture of multiple sclerosis seems to grow by the month. Therefore I just wonder whether most would see the details on MR provided in such tomes as MacAlpine's or Raines' multiple sclerosis sufficient without investing a further £50.

NEIL ROBERTSON

**Parkinson's Disease. (Advances in Neurology, Volume 69).** Edited by LEONTINO BATTISTIN, GUGLIELMO SCARLATO, TOMMASO CARACENI, and STEFANO RUGGIERI. (Pp 640; £127.00). Published by Lippincott Raven Publishers, New York, 1995. ISBN 0-7817-0341-7.

This book covers most aspects relating to the neurobiology of Parkinson's disease and closely related conditions and arose from the 11th International Symposium on Parkinson's disease held in March 1994. These meetings are held every three years and are recognised as one of the major international symposia on these conditions and this book is filled with contributions from current international figures in this field. Nearly half the book is devoted to epidemiological, biochemical, and pathophysiological aspects of Parkinson's disease and related conditions, reflecting current interests worldwide. Inevitably, it seems that collections of papers arising from a large meeting contain anomalies of structure, and this one is no exception. However, one benefit may be balance in terms of representation of current views and this is achieved in the representation of both sides of the "genes or environment" question. Clinical aspects focus particularly on the "Parkinson plus" syndromes and dementia in Parkinson's disease, with separate sections on autonomic disorders, and neuroimaging, and the last section deals with therapeutic aspects. Although this section is probably now more out of date than any of the others, there are chapters on most of the major pharmacological treatments and there is a particularly helpful outline of therapeutic controversies. This section also covers thalamotomies, pallidotomies, and subthalamic stimulation, but strangely there is no separate chapter on neural transplantation. Overall this is a useful and interesting book for anyone with an interest in extrapyramidal syndromes.

ANNE ROSSER

## CORRECTION

Canavero S, Bonicalzi V, Ferroli P. Can trauma alone to the trigeminal root relieve trigeminal neuralgia? The case against the microvascular compression hypothesis. *J Neurol Neurosurg Psychiatry* 1997;**63**:411.

In line 7 of the first paragraph, "asymptomatic" should read "symptomatic".

The part sentence starting 10 lines from bottom, first column "five with arachnoiditis, two with a sharp root kink, four distally (group 4)." should read "three with arachnoiditis, two with a sharp root kink, all distally (group 4)".