can not only show "some abnormality that encourages angiographic examination" but can also diagnose dissections involving the pretransverse, C6–C5 and C5–C4 intertransverse segments of the VA.[5] The diagnosis is based on the association of a localised increase in arterial diameter with haemodynamic signs of stenosis or occlusion and/or decreased pulsatility and intravascular echoes at the same level. Furthermore, ultrasonic examination is an excellent tool for the follow up of dissection.

6) Among other diagnostic procedures, the authors did not mention thin-section contrast-enhanced dynamic CT scan and MRI. By virtue of its sensitivity to both blood flow and thrombus formation, its multiplanar imaging capability, and its noninvasiveness, MRI (and soon MR angiography) is becoming the imaging modality of choice for the evaluation of suspected carotid or vertebral dissection (fig). At present, however, MRI does not assist in distinguishing between intraluminal and intramural thrombus and therefore does not allow the diagnosis of occlusive forms of vertebral dissection.

7) The relation of trauma to dissection is a complex issue. Hinse *et al*[1] considered their patient 4 as an example of traumatic (chiropractic manipulation) dissection. We recently reported[6] the case of a woman with a 3 week history of cervical pain who developed iscaemia in the basilar artery territory following cervical manipulation. Necropsy revealed 2 VA dissections, a recent one probably due to cervical manipulation and a second one, a few weeks old, accounting for the initial cervical pain. This case demonstrates that cervical pain that precedes and motivates chiropractic manipulation may be the first symptom of a hitherto unrecognised spontaneous (or traumatic) dissection and illustrates the difficulty in classifying with certainty whether dissection is spontaneous or traumatic.

Apart from trauma and fibromuscular dysplasia, other conditions implicated as risk factors for dissection include migraine, oral contraceptives, and chronic high blood pressure. In a case control study,[7] we found a significant positive association of dissection with migraine and current oral contraceptive use but not with hypertension. However, the mechanisms leading to this association remains speculative.

8) Finally, we agree that anticoagulants are not harmful in extracranial VA dissection and may even be of benefit although no conclusion can be drawn from the comparison of nonrandomised treatment groups.

JEAN-LOUIS MAS
Hôpital Ste-Anne,
75674 Paris Cedex 14,
France

M G BOUSSER
P J TOUBOUL
Hôpital Saint-Antoine,
75571 Paris Cedex 12,
France

1 Hinse P, Thie A, Lachenmayer L. Dissection of the extracranial vertebral artery: report of four cases and review of the literature. *J Neurol Neurosurg Psychiatry* 1991;**54**:863–9.
2 Mas JL, Bousser MG, Hasboun D, Laplane D. Extracranial vertebral artery dissections: a review of 13 cases. *Stroke* 1987;**18**:1037–47.
3 Mokri B, Houser OW, Sandok BA, Piepgras DG. Spontaneous dissections of the vertebral arteries. *Neurology* 1988;**38**:880–5.
4 Hart RG. Vertebral artery dissection. *Neurology* 1988;**38**:987–9.
5 Touboul PJ, Mas JL, Bousser MG, Laplane D. Duplex scanning in extracranial vertebral artery dissection. *Stroke* 1987;**18**:116–21.
6 Mas JL, Henin D, Bousser MG, Chain F, Hauw JJ. Dissecting aneurysm of the vertebral artery and cervical manipulation: a case report with autopsy. *Neurology* 1989;**39**:512–5.
7 D'Anglejan-Chatillon J, Ribeiro V, Mas JL, Youl BD, Bousser MG. Migraine—A risk factor for dissections of cervical arteries. *Headache* 1989;**29**:560–1.

Hinse and Thie reply:

We thank Dr Mas and colleagues for their interest in our recent paper,[1] and we appreciate the opportunity to comment on a few of the issues raised by them.

Our paper did not deal with the incidence of vertebral artery (VA) dissection which remains unknown. Better diagnosis and systematic study will hopefully shed more light on incidence of this condition in the future. In our analysis, we have included only case reports providing sufficient detail of the individual patient, but not summarised series, thus the results of Mokri *et al*[2] were not considered. We apologise for not including the well documented patients by Mas *et al*.[3]

The question of internal carotid artery (ICA) dissection was not the subject of our paper. We agree that angiographic visualisation of all four brain-supplying vessels should be attempted in acute VA dissection in order not to miss concomitant asymptomatic ICA dissection. This point is of particular importance in spontaneous VA dissection: in 5 of 29 reviewed patients concomitant ICA dissection was documented, but not in 28 patients with traumatic VA dissection.

Mas *et al* correctly state that dissection as a cause of arterial occlusion may be hard to diagnose. However, the angiographic appearance of tapering occlusion is highly suggestive of dissection.[4] In our patients, complete recanalisation of a formerly occluded VA (cases 2 and 3) and visualisation of a small pseudoaneurysm (case 2) made the diagnosis of VA dissection highly probable.

The value of ultrasound method in the diagnosis of VA dissection remains to be determined. Our own experience[1] and the work of Touboul *et al*[5] on three patients examined by duplex scan are too preliminary to allow any firm conclusions. As we have pointed out in our paper, ultrasound methods may be suitable for diagnosis of recanalisation, possibly obviating the need for repeated angiography in some patients. The same holds true for modern neuroimaging methods. Contrast-enhanced CT scan and MRI may corroborate the diagnosis of VA dissection, and are also increasingly recommended for follow up studies. However, both methods do not allow examination of the affected vessels in their entire length. These neuroimaging techniques will have to prove their value in a systematic study against the present "gold standard" (angiography).

The role of many presumably predisposing conditions, in particular migraine, use of oral contraceptives or hypertension, remains totally obscure. It is speculative whether some of these factors might act by merely facilitating the occurrence of stroke after dissection, but not dissection itself. It is also unknown why minor trauma may induce cervical dissections in some patients at any particular time, but why recurrences in these patients are rare.

P HINSE
A THIE
Department of Neurology,
University of Hamburg,
Martinistr 52,
2000 Hamburg 20, Germany

1 Hinse P, Thie A, Lachenmayer L. Dissection of the extracranial vertebral artery: report of four cases and review of the literature. *J Neurol Neurosurg Psychiatry* 1991;**54**:863–9.
2 Mokri B, Houser OW, Sandok BA, Piepgras DG. Spontaneous dissections of the vertebral arteries. *Neurology* 1988;**38**:880–5.
3 Mas JL, Bousser MG, Hasboun D, Laplane D. Extracranial vertebral artery dissections: a review of 13 cases. *Stroke* 1987;**18**:1037–47.
4 Mokri B. Traumatic and spontaneous extracranial internal carotid artery dissections. *J Neurol* 1990;**237**:356–61.
5 Touboul PJ, Mas JL, Bousser MG, Laplane D. Duplex scanning in extracranial vertebral artery dissection. *Stroke* 1987;**18**:116–21.

Late onset globoid cell leukodystrophy

I read with great interest the paper by Grewal *et al*.[1] I would like to add a few comments.

First, the authors suggest that their patient's late onset (at age 14) distinguishes his disease from globoid cell leukodystrophy (GLD) distinct from the infantile and late infantile onset types. This may be true for the first type, but the latter can occur within one family together with a later onset type.[2]

Second, it would be interesting to know whether the white matter hyperintensities on the MRI were diffuse or rather restricted to the occipito-parietal white matter, as described in other late onset GLD.[2 3] If so, this posterior white matter involvement on MRI would seem to be very useful to distinguish GLD from other cerebral white matter diseases.

PETER VERDRU
Neurologie,
Universitaire Ziekenhuizen,
Herestraat 49,
3000 Leuven, Belgium

1 Grewal RP, Petronas N, Barton NW. Late onset globoid cell leukodystrophy. *J Neurol Neurosurg Psychiatry* 1991;**54**:1011–2.
2 Verdru P, Lammens M, Dom R, Van Elsen A, Carton H. Globoid cell leukodystrophy: a family with both late-infantile and adult type. *Neurol* 1991;**41**:1382–4.
3 Shapiro EG, Lockman LA, Krivit W. Correlation of Magnetic Resonance Imaging and Neuropsychological Abnormalities in Late-onset Leukodystrophies. *Ann Neurol* 1991; **30**:466–7.

Aseptic meningitis associated with high dose intravenous immunoglobulin therapy

We read with great interest the report by Watson *et al*[1] and we would like to draw the authors attention to a similar case we published last year.[2]

Our patient was a seven year old boy with idiopathic thrombocytopenic purpura who had well-documented episodes of acute aseptic meningitis on two occasions after the second intravenous dose of immune globulin. On these two occasions, the patient developed aseptic meningitis on day three; quite identical to the two patients reported by Watson, whereas Kato's patient developed the aseptic meningitis two days after a five day course of intravenous immune globulin therapy.[3]

In our patient the immune globulin preparation used was Sandoglobulin IV (Sandoz), which is a formulation prepared by cold ethanol fractionation. It was given at a dose of 0·4 g per kilogram of body weight infused over a 11 hour period.

From these three reports, we conclude:
1 Intravenous immune globulin can induce aseptic meningitis in children as well as in adults: the strong temporal association (on day three in our patient and in Watson's patients) and the repetitive occurrence in the same patient (on two occasions in Kato's patient and in our patient) are both strong arguments in favour of this. It should no longer be a hypothesis.
2 Several preparations of intravenous immune globulin can induce aseptic meningitis. Up till now it has been reported with four different preparations: with immunoglobulin prepared with polyethylene glycol and with a sulphonated preparation,[3] with a formulation prepared by cold ethanol fractionation (Sandoglobulin)[2] and with a low PH formulation prepared with ethylene glycol (Intragam).[1]
3 As with many other iatrogenic diseases, the aseptic meningitis in itself is rather benign and resolves rapidly with cessation of the therapy. But not recognising this complication as such might result in potentially dangerous and/or unnecessary explorations (lumber puncture in a thrombocytopenic patient;[4] CT scan)

The possible occurrence of aseptic meningitis following immune globulin infusion should thus be known by all physicians and should be mentioned by the pharmaceutical firms.

M CASTEELS-VAN DAELE
L WIJNDAELE
P BROCK
M KRUGER
Department of Paediatrics, University Hospital Gasthuisberg, 3000 Leuven, Belgium

Ph GILLIS
Department of Paediatrics, Virga Jesse Ziekenhuis, 3500 Hasselt, Belgium

1 Watson JD G, Gibson J, Joshua DE, Kronenberg H. Aseptic meningitis associated with high dose intravenous immunoglobulin therapy. *J Neurol Neurosurg Psychiatry* 1991; 54:275–76.
2 Casteels-Van Daele M, Wijndaele L, Hunninck K, Gillis Ph. Intravenous immune globulin and acute aseptic meningitis. *N Engl J Med* 1990;323:614–5.
3 Kato E, Shindo S, Eto Y, *et al.* Administration of immune globulin associated with aseptic meningitis. *JAMA* 1988;259:3269–71.
4 Scott EW, Cazenave CR, Virapongse C. Spinal subarachnoid hematoma complicating lumbar puncture: diagnosis and management. *Neurosurgery* 1989;25:287–93.

Dr Watson *et al*[1] described two patients who developed aseptic meningitis after high dose intravenous immunoglobulins (IgIV). Both had mild symptoms and recovered completely within 14 and seven days, respectively. We consider it important that this side effect has been noted. It improves detection of future similar effects and places it in the appropriate pathogenetic context. The observations on these two patients, however, do not give any clue about the incidence of this side effect.

In the Dutch Multi Centre Guillain-Barré trial we compared high dose IgIV with plasma-exchange (PE). Based on the main outcome criterion—functional improvement four weeks after randomisation—IgIV was superior to PE.[2 3] As a result of this study IgIV may well be used more often in neurological patients after detailed publication of the results. We would therefore like to report our experiences on the side effects of IgIV.

In 74 patients 0·4 g/kg of IgIV (Gammagard^{R}, Hyland Division, Baxter) was infused during five consecutive days, a total of 370 infusions. These infusions were all performed during the acute phase of the Guillain-Barré syndrome in patients of all ages. During the infusion period patients were scored every other day and questions about complications were included in the datasheets. A treatment form was also filled out, and this included questions about any unusual event during treatment.

Five time-related events occurred during these 370 infusions; blood pressure dropped but did not need any treatment (2), dyspnoea treated with a diuretic (1), temperature increase treated with clemastine (1) and transient macroscopic haematuria (1). The treatment course was not interrupted in any of the cases. The last event may have been coincidental, but the others may have been caused by the IgIV infusions. They were, however, mild and transient. Aseptic meningitis was not observed in any of the patients. We conclude that the incidence of side effects of high dose IgIV is low and that IgIV may be safely applied in neurological patients.

FGA VAN DER MECHÉ
RP KLEYWEG
Coordinatiecentrum Guillain-Barré Trial, Afdeling Neurologie, Kamer Ee 2222, Medische Faculteit, Erasmus University, Rotterdam, The Netherlands

1 Watson JDG, Gibson J, Joshua DE, Kronenberg H. Aseptic meningitis associated with high dose intravenous immunoglobulin therapy. *J Neurol Neurosurg Psychiatry* 1991;54:275–6.
2 Van der Meché FGA, Kleyweg RP, Meulstee J, Schmitz PIM and the Dutch Guillain-Barré Study Group. *The Dutch Guillain-Barré trial comparing high-dose immunoglobulins with plasma-exchange; preliminary results.* Oxford: Peripheral Neuropathy Association of America (PNAA), 1990.
3 Van der Meché FGA, Kleyweg RP, Meulstee J, Schmitz PIM and the Dutch Guillain-Barré Study Group. *The Dutch Guillain-Barré trial comparing high-dose immunoglobulins with plasma-exchange.* VII Int Congress on Neuromuscular Diseases, Munich, 1990.

The brain in schizophrenia

The excellent editorial by Ron and Harvey[1] notes that "to have forgotten that schizophrenia is a brain disease will go down as one of the great aberrations of twentieth century medicine". However, I think it is open to question as to whether schizophrenia can be considered as a brain disease in the same way as established brain diseases such as viral or atrophic disorders of the CNS. There may be more general reservations with the validity of the concept of schizophrenia itself,[2] but I have four specific reservations with calling schizophrenia a brain disease:
1) Unlike most brain diseases, there is as yet no diagnostic pre- or post-mortem biological or other physical marker for schizophrenia.
2) Compared to most brain diseases, there is no predictable pattern of deficit in sensory or motor functions or in "primitive" reflexes.
3) Unlike most brain diseases, psychological or psychosocial variables play a significant part in the aetiology and stability of outcome of many patients with schizophrenia.
4) The relationship between neurobiological features of patients with schizophrenia and the pattern or severity of psychiatric disturbance is much more equivocal than in the case of analagous relationships in brain diseases.

At present I would therefore feel comfortable in calling schizophrenia a brain *dysfunction*, but I do not think there is yet sufficient evidence to call it a brain disease. It is possible that the term disease, if commonly applied to schizophrenia, may in the perception of some clinicians limit the range of viable therapeutic options.

NARINDER KAPUR
Wessex Neurological Centre, Southampton

1 Ron MA, Harvey I. The brain in schizophrenia. *J Neurol Neurosurg Psychiatry* 1991;53: 725–6.
2 Boyle M. *Schizophrenia: a scientific delusion.* London: Routledge, 1990.

(^{99m}Tc)-HM-PAO SPECT and dementia in Parkinson's disease

With great interest we read the article from Spampinato *et al*[1] and we would like to comment on some aspects of the article.

We performed single photon emission computed tomography (SPECT) using (^{99m}Tc)-HM-PAO as a tracer in 5 clinically demented and 6 non-demented patients with Parkinson's disease (PD). HM-PAO uptake was measured in the frontal, parietal and temporo-parietal cortex and was expressed as cortical/cerebellar activity ratio. None of our patients had a reduction of HM-PAO uptake of more than 20%, which seems to be in concordance with Spampinato *et al*. In contrast to Spampinato *et al*, however, we found no difference between the demented and non-demented PD patients. We investigated whether there was a relation between SPECT-scan data and neuropsychological tests in our group as a whole (n = 11). Using the Spearman rank correlation test, we found no significant correlations between neuropsychological perfomance and SPECT data on any test.

One of the main problems in our research was the estimation of dementia in PD. Of the 5 patients who fulfilled the criteria for dementia as described in the DSM-III-R, all lacked typical cortical features. All of our patients were able to undergo the neuropsychological tests. In the study by Spampinato *et al*, diagnosis of dementia was based on neuropsychological assessment, according to which the PD patients were divided into two groups of 15 patients. However, five of their patients could not be tested, probably due to severe dementia. It was not stated by the investigators whether their demented PD patients were free from cortical features.

In our opinion, one of the possible explanations for the differences in results is that patients had no cortical dysfunction and therefore no Alzheimer-like pathology. Further elucidation of dementia as seen in PD seems mandatory.

MA KUIPER
HC WEINSTEIN*
PLM BERGMANS
Ph SCHELTENS
E Ch WOLTERS
Department of Neurology and Psychiatry of the Free University Hospital Amsterdam, Amsterdam, The Netherlands*

1 Spampinato U, Habert MO, Mas JL, Bourdel MC, Ziegler M, de Recondo J, Askienazy S, Rondot P. (^{99m}Tc)-HM-PAO SPECT and cognitive impairment in Parkinson's disease: a comparison with dementia of the Alzheimer type. *J Neurol Neurosurg Psychiatry* 1991; 54:787–92.