indirect immunofluorescent test for Lyme disease (Institut Pasteur, Paris), Rose Bengal Plate test, immunoelectrophoresis and IgG secretion index. After the last episode electrophysiological studies (motor conduction velocity and F wave latency in the legs, brainstem auditory evoked responses, visual evoked responses) and a cerebral and whole spinal cord MRI scans were all normal.

Our patient had recurrent meningomyelitis and latterly encephalitis, in which each episode was preceded by fever and myalgia and developing severe neurological deficits requiring, on one occasion, mechanical ventilation. In spite of the severity of the motor and sensory dysfunction there was always complete recovery. The initial CSF inflammatory profile was the only abnormality found. All the other repeated investigations were normal or negative. We can only find one similar report in the literature.[1]

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1 Tippet DS, Fishman PS, Panitch HS. Relapsing transverse myelitis (abstr). *Ann Neurol* 1988; 24:143.

Creutzfeldt-Jacob disease following cadaveric dura mater graft

There have been three previous reports of Creutzfeldt-Jacob disease (CJD) following repair of dural defects by surgical grafting of commercially prepared, lyophilised cadaveric dura mater, one each from USA,[1] New Zealand[2] and Italy.[3] We have recently seen the first case of CJD in the United Kingdom presumed to have been transmitted by cadaveric dura mater graft.

In October 1985 a 26 year old man had a foramen magnum decompression and cervical laminectomy for syringomyelia and cerebellar ectopia. During the procedure a dural graft was stitched from the level of the third cervical vertebra to the occiput. Postoperatively he had a spastic gait and an ataxic left arm with spinothalamic sensory loss, but he remained independent and worked as a builder. In August 1989, at the age of 30, he became increasingly withdrawn: he had difficulty recognising people, and his speech, comprehension and balance became disturbed. On admission to hospital in September 1989 he was alert but severely dysphasic and dysarthric. He had a spastic tetraparesis and ataxia of all four limbs. He was unable to feed himself or walk unaided. Haematological and biochemical investigation and enhanced CT brain scan were normal. The cerebrospinal fluid was acellular with protein 0·9g/l and normal glucose. He deteriorated and became drowsy, mute, increasingly ataxic, and developed frequent myoclonic jerks. The electroencephalogram evolved into a pattern of intermittent repetitive triangular wave complexes on a background of generalised irregular slow-frequency activity characteristic of CJD. He died in December 1989, four months after the onset of symptoms.

Histological examination of the brain showed widespread spongiform degeneration with gliosis and neuronal loss involving the neocortex, striatum and cerebellum.

This patient's illness began 46 months after insertion of the dural graft, compared with intervals of 19, 31, and 44 months for the other three reported cases who were 28, 25 and 27 years old respectively. All four patients are considerably younger than the mean age of 63 years for sporadic cases occurring in the UK in whom no aetiological factors have been identified.[4] They had all received the same type of lyophylised human cadaveric dural graft, "Lyodura", manufactured by B Braun Melsungen AG, Germany, and all the grafts were inserted within a 20 month period between May 1985 and November 1986. The transmissible agent thought to be responsible for CJD is resistant to inactivation by boiling, 10% formaldehyde and ultraviolet or ionizing radiation, but it can be inactivated by autoclaving at 134C for 18 minutes, or by immersion in 1 molar NaOH for one hour. The latter treatment has been incorporated into the manufacture of "Lyodura" since 1987.[3,5] Since its introduction in 1969, over half a million packages of "Lyodura" have been used but only four cases of CJD in this group of patients have been reported to date: the risk of CJD related to "Lyodura" therefore seems low.

The implications arising from these cases are clear: autologous graft material should be used where possible. Appropriate standards should be applied in selection and preparation of donor material and physicians should be alert to this relationship in patients with a previous history of neurosurgery who develop a dementing illness.

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MATTERS ARISING

Ticlopidine, a new anti-thrombotic drug

In your editorial[1] Charles Warlow answers the question: "Ticlopidine, a new anti-thrombotic drug: but is it better than aspirin for long term use?". The editorial gives a lot of important information. I would, however, like to make several comments:

1) Professor Warlow says that there has been no large trial of aspirin alone in major ischaemic stroke. In one of the large secondary prevention trials of ischaemic lesions of the nervous system, in the European Stroke Prevention Study 1 (ESPS 1), where the prevention was due to the association dipyridamole-aspirin, two thirds of the patients were included after major stroke (that is, a stroke with neurological symptoms lasting more than seven days). The results obtained can add some information to the remarks made in the editorial.

Seven hundred and thirty eight post-stroke patients were included in the placebo group and 764 in the group receiving the active drug or 75 mg dipyridamole and 330 mg acetylsalicylic acid three times daily. In the first group, there were 196 end-points (a new stroke or death) and in the active arm, there were only 138 end-points, a reduction of 29·6%, which is highly significant ($p < 0.001$).

2) In the ESPS 1, side effects were mainly due to the high dose of acetyl-salicylic acid (990 mg per day), but toxic effects were almost non-existent. This is not the case with ticlopidine treatments.

In conclusion, we can say that secondary prevention of ischaemic lesion of the nervous system is possible thanks to anti-aggregating agents. Among the anti-aggregating agents, the association of dipyridamole and acetylsalicylic acid gives the ESPS 1 the best results. This association also works after major stroke and gives less side-effects than ticlopidine.

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1 Warlow C. Ticlopidine, a new anti-thrombotic drug: but is it better than aspirin for long-term use? (Editorial). *J Neurol Neurosurg Psychiatry* 1990;53:185–7.

Warlow replies:

I am relieved that Dr Lowenthal agrees with me that there have been no large trials of aspirin alone in major ischaemic stroke and I certainly do not disagree with him that the European Stroke Prevention Study I (ESPS I)[1] trial recruited a large number of major stroke patients. The ESPS I trial does not, of course, tell us anything about aspirin *alone* since it tested the combination of aspirin with dipyridamole against placebo. So far, in the Antiplatelet Trialists' Collaboration, there is no indirect or direct evidence that this combination of drugs is more or less effective than aspirin alone.[2] If Dr Lowenthal *really* believes that the combination of aspirin and dipyridamole gives the best results then he should certainly prescribe it, whatever I or anyone else believe to be the correct interpretation of the data; it would be unethical not to do so. However, since he coordinates the ESPS II trial, I presume that he considers it ethical for other physicians to randomly allocate patients in that trial to placebo, aspirin alone and dipyridamole alone as well as to the combination of aspirin and dipyridamole.

I am not too sure what the difference is between "side effects" and "toxic effects" but I, like Dr Lowenthal, emphasised that the adverse effects of ticlopidine were considerably more common than those of aspirin.

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1 The ESPS Group. The European Stroke Prevention Study (ESPS) principal endpoints. *Lancet* 1987;ii:1351–4.

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Cognitive impairments and depression in Parkinson's disease

Starkstein *et al*[1] present a follow up study of depression and cognitive impairment in Parkinson's disease (PD). Central to the concept of this paper is the meaning of the term "depression". The literature concerning affective disorder and PD uses the term inconsistently. Variously, it has referred to a general clinical opinion of a morbid state; to a state diagnosed by the summation of symptoms and signs greater than a cut-off score on an ordinal rating scale; and to a clearly defined syndrome as described in DSM III "Major Depression". The latter usage is preferable. "Major Depression" has been criticised because "many physically sick individuals could be included simply on account of their physical illness and without the necessity to postulate the presence of mental disorder".[2] Of the additional features (in addition to lowered mood) which are required to diagnose "Major Depression", most can occur solely as a result of PD. Dakof and Mendelsohn[3] stated "For Parkinson patients, many of these symptoms are likely to be part of the primary pathology of parkinsonism and not an indication of depression. At present, there is no way to make a distinction".

Starkstein *et al* do not appear to have appreciated these difficulties. They used a very low cut-off (7 and above) on the HDRS, an ordinal rating scale. About half the items on the HDRS could be confused by the cross over of the features of affective disorder and PD. They validated this against DSM-III "Major Depression" which has problems as described above. Furthermore, the DSM III diagnosis was made by using the PSE which generates diagnoses from ICD-9 rather than DSM-III. This procedure should be validated itself before being used as a "gold standard" for validating the HDRS, as the two classificatory systems differ radically regarding depressive syndromes. Hence "depression" as diagnosed by Starkstein *et al* is unlikely to bear any resemblance to any condition diagnosed by psychiatrists. The finding of significantly more tremor, akinesia and rigidity in the depressed group is consistent with the notion that higher HDRS scores are associated with more severe PD, and do not necessarily reflect the presence of a depressive disorder. The low levels (in numbers and dosage) of treatment in the depressed group suggests that the overall degree of morbidity was low.

Further confusion arises from the method of use of MMSE scores. The authors use the MMSE score itself rather than the cut-off of 23 as stated. The use of mean values makes it difficult to determine the clinical significance of the changes reported because of the ceiling effect of its maximum value of thirty. The important information clinically is how many people become demented during follow up. In table four the large standard deviation for the last mean for MMSE in the depressed group suggests some subjects obtained very low scores accounting for the differences in the means. This use of parametric statistics for data which is non-parametric in nature is not appropriate.

These factors greatly reduce the value of the findings of this study. Unless the confusion surrounding the definition and diagnosis of affective disorder and cognitive impairment are resolved, it is unlikely that issues in this area will be clarified.

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1 Starkstein SE, Bolduc PL, Mayberg HS, Preziosi TJ, Robinson RG. Cognitive impairments and depression in Parkinson's disease: a follow up study. *J Neurol Neurosurg Psychiatry* 1990;**53**:597–602.
2 Snaith RP. The concepts of mild depression. *Br J Psychiat* 1987;**150**:387–93.
3 Dakof GA, Mendelsohn GA. Parkinson's disease: the psychological aspects of a chronic illness. *Psycholog Bull* 1986;**99**:375–87.

Starkstein et al reply:

Madeley *et al* raise several points regarding our study. They make the important observation that major depression should be diagnosed based on diagnostic criteria, such as in DSM-III. We certainly agree with this observation, and we acknowledged in the paper the limitation of using a cut-off score on a depression scale. However, in a recent study in which we used DSM-III criteria, we found similar results, for example, patients with PD and major depression showed a significantly faster cognitive decline than patients with PD and no depression (Starkstein *et al*, unpublished).

The second issue raised by Madeley *et al* is also an important one. Whether depression can be reliably diagnosed in the presence of a neurological disorder has been recently examined by our group.[1-2] For PD, we found we can diagnose depression using slightly modified DSM-III criteria for major depression with a sensitivity and specificity of 91% and 100% respectively. Thus we are confident that our diagnosis is not clouded by the presence of the extrapyramidal symptoms of PD.

Even after using non-parametric data, depressed patients showed a significantly faster cognitive decline. Eight of the 18 depressed patients (44%) had a follow up MMSE score in the abnormal range, compared with three of the 31 non-depressed patients (10%) ($X^2 = 7{\cdot}90$, df = 1, $p < 0{\cdot}005$).

We believe the low number of depressed patients with PD receiving treatment for depression is not the consequence of a low degree of morbidity, but the fact that depression may not be diagnosed unless a standardized psychiatric evaluation is used.

Finally, the finding of significantly more severe tremor, rigidity and akinesia in the depressed compared to the non-depressed group is the result of a significantly longer duration of illness. In support, when depressed and non-depressed patients were matched for duration of illness, no significant between-group differences in tremor, rigidity, and akinesia were observed (paired $t = 1{\cdot}62$, $0{\cdot}34$, $0{\cdot}72$, respectively $p = NS$).

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1 Fedoroff JP, Lipsey JR, Starkstein SE, Forrester A, Price TR, Robinson RG. Phenomenological comparison of major depression following stroke, myocardial infarction and spinal cord lesions. *J Affect Dis* 1990 (in press).
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Misconceptions and inappropriate use of terms in hyperthermic syndromes

Progress in understanding the pathophysiology of hyperthermic syndromes is hampered, as much of the literature on neuroleptic malignant syndrome (NMS) is polluted with inadequate terms and thermoregulatory misconceptions. A previously published paper on the subject is also open to criticism.[1]

In the first place, the term fever is applied to describe the condition, in which a patient's body temperature is elevated. Second, fever or (hyper) pyrexia and hyperthermia are used as synonyms. Fever or pyrexia results from a hypothalamic controlled elevation of the temperature setpoint. Through coordinated physiological and behavioural responses the body temperature rises until the setpoint is reached.[2] Hyperthermia is defined as the elevation of body temperature above setpoint, occurring when heat-dissipating mechanisms are defective or insufficient in relation to the internal heat production or excessive environmental heat.[2] Therefore, elevated body temperatures in cases of NMS should be designated as "hyperthermia".

Also, the term "autonomic dysfunction" is used, describing the autonomic responses (tachycardia, diaphoresis, flushing, and tachypnoea), in patients with hyperthermia.[1] In view of thermoregulation these profound autonomic responses can only be considered adequate in response to the elevated body temperature.

Furthermore, disruption of dopaminergic thermoregulatory mechanisms in the hypothalamus is frequently implicated in the development of hyperthermia in NMS.[1] We think this hypothesis is not justified because in NMS hyperthermia is due to increased muscular heat production, secondary to increased rigidity with tonic contractions following dopaminergic-receptor blockade in the basal ganglia. This is supported by the beneficial effects of the directly acting muscle relaxant sodium dantrolene used in some of the cases with NMS.[3]

The elevated body temperature is associated with pronounced, and thus adequate (hypothalamic controlled) autonomic responses trying to cope with the heat excess. Concerning the clinical spectrum of hyperthermic syndromes, neuroleptic malignant syndrome (NMS) is becoming a most inappropriate name, used in some cases. While the NMS may take a severe, potentially lethal course, the designation "malignant" hardly seems appropriate in the majority of the cases.[4,5]

The occurrence of hyperthermic syndromes in Parkinsonian patients strongly resembles NMS. This signifies that impaired central dopaminergic activity in the basal ganglia is the hallmark of a continuum of hyperthermic syndromes, which should