LETTERS TO THE EDITOR

Lack of association between macrocytosis and multiple sclerosis

An increase in red cell diameter in patients with multiple sclerosis (MS) compared with normal controls was described by Plum and Fog in 1959.¹ Interest in this subject has been reawakened by reports indicating that patients with MS had mild but significant macrocytosis compared with an age- and sex-matched neurological control group.^{2,3} The cause of the macrocytosis is unknown, but some observations have suggested a possible disturbance in vitamin B12 metabolism, binding or transport.⁴ We have compared haematological records of patients with definite MS with those of an individually matched neurological control group.

This study was based on a population of 154 consecutive patients, who satisfied the Poser criteria for clinically or laboratory definite MS. Patients with possible MS were not included. The mean (SD) disease duration was 8.4 (7.9). The mean Kurtzke Expanded Disability Status Scale (EDSS) was 2.9 (1.9). All patients provided blood samples before specific therapy was started.

The control group consisted of 154 patients with miscellaneous neurological and psychiatric disorders which included: cerebrovascular lesions, headache, mechanical cord and nerve root lesions, trigeminal neuralgia, vestibular disease, and anxiety disturbances. Patients with subacute combined degeneration or neuropathies were excluded on the basis of a possible vitamin B12 or folate deficiency.

Red cell counts, haemoglobin (Hgb), haematocrit (Hct) and mean cell volume (MCV) were measured using the Coulter Blood Counter. Demographic and haematological characteristics of the MS patients and of the control group are shown in table 1.

No significant differences between the two groups were found in any of the measures considered (two tailed Student's *t* test), nor was any difference observed when comparing MS female and male patients with their respective sexes in the controls. The mean reference value for MCV of our laboratory is 90 fl (range 80 to 99 fl). Forty three MS patients showed a value higher than the mean of laboratory range compared with 40 control subjects. This difference was not significant. Only one patient in each group had an MCV higher than the normal laboratory range. No

linear correlation was found between haematological measures and EDSS or disease duration (Pearson Product Moment Correlation Coefficient). Twenty six patients had an MS history of less than 1 year. This clinical subgroup did not show any significant difference in MCV when compared with neurological controls or with MS patients who had a longer disease duration.

Our results obtained in a relatively large population do not support previous findings of a significant association between MS and macrocytosis.^{2,3} In spite of recent evidence which indicates macrocytosis as an early phenomenon in the course of the disease³ we did not observe any macrocytosis in the clinical subgroup of patients with short disease duration (< 1 year). Since our study did not differ from previous ones either in the clinical design or in the characteristics of the neurological control group other possible explanations which may account for these discordant findings must be considered. Plum and Fog¹ suggested that the Price-Jones curve in MS patients was similar to that seen in pernicious anaemia (PA). Furthermore, PA is reported to have geographic, racial and genetic distribution similar to MS.² In particular Najim Al-Din *et al*³ observed that MS and PA share the same HLA pattern (HLA A3-B7-DR2).

However, MS patients from Central and Southern Italy are more likely to show HLA DR4 and DR5 instead of HLA DR2.⁵ The

lack of association therefore between MS and macrocytosis observed in this study may be attributed to the fact that the genetic background of our population is different from that of previous studies.

Alternatively macrocytosis may be due to an associated disorder or a coincidental finding rather than a deficit specifically related to the disease.

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The IMAO-B MDL 72.974 A in Parkinson's disease

The MAO-B inhibitor selegiline has been reported to potentiate levodopa treatment and to prevent the progression of disability in early Parkinson's disease.^{1,2} MDL 72.974 A is a new potent, selective, enzyme-activated irreversible inhibitor of MAO type B.³ Five patients in stage III-IV Parkinson's disease with motor oscillations and dyskinesias were studied. Mean (SD) age at onset was 46 (6) years, duration of the disease was 6 (2) years. All patients exhibited a significant improvement in their motor performance in response to levodopa therapy [mean (SD) daily dose, 750 (200) mg] plus a dopa-decarboxylase inhibitor. Motor disability was evaluated using the motor subscale of the UPDRS.⁴ The baseline score (at the time of maximal disability without treatment) and the treated score (at time of maximal clinical improvement) were recorded. In all patients all regular drugs were withheld 18 hours before evaluation of motor response to a single supraliminal morning dose of levodopa⁵ [160 (20) mg] (mean of 2 tests). During the test, Parkinsonian disability was rated before and 15, 30, 45, 60, 90, 120, 150, 180, 240 minutes after drugs administration. Patients then received MDL 72.974 A (4 mg) once a

day in addition to levodopa and other regular anti-Parkinsonian drugs (anticholinergic and dopamine agonists) for 3 weeks. No modification of doses was allowed during this period. At the end of the period, the motor response to the same supraliminal morning dose of levodopa plus MDL 72.974 A was assessed (mean of 2 tests) under the same conditions as described above. The effects (delay of onset, duration of action, improvement in motor disability score, dyskinesia score) of levodopa alone and of MDL 72.974 A administered simultaneously with levodopa were compared.

After the 3 weeks of combined treatment, the baseline motor score disability was significantly improved (table). A significant prolongation of the duration of "on" response with MDL 72.974 A (4 mg) plus levodopa was observed on the acute challenge study, after 3 weeks of sustained treatment (table). Such differences were not observed when the dose of MDL 72.974 A was of 1 mg (not shown). Dyskinesias were similar in intensity to those experienced with levodopa alone but the duration was longer. Adverse effects consisted of postural hypotension (*n* = 3), transient facial flush (*n* = 1), dry mouth (*n* = 2), gastralgia (*n* = 1). No haematological or biochemical changes occurred.

Table Demographic and haematological characteristic in MS and neurological controls

	Multiple Sclerosis (N = 154)	Neurological Controls (N = 154)
Mean (SD) age (years)	35.9 (11.2)	35.9 (11.6)
Sex ratio	50:104	50:104
Male:Female		
Red cell count (× 10)	4.70 (0.45)	4.68 (0.46)
Hgb (g/dl)	13.96 (1.47)	13.91 (1.50)
Hct	40.60 (3.80)	40.30 (4)
MCV (fl)	86.57 (6.4)	86.36 (6.2)

Table Effect of a single oral dose of levodopa without or with MDL 72.974 A (4 mg) on Parkinsonian disability

	Motor disability score		Response timings (min)	
	Baseline	Treated	To onset	Duration
Levodopa	38.5 (20.1)	12.9 (5.6)	40.7 (8)	122 (20)
Levodopa + MDL 72.974 A	32.0 (16.8)*	10.6 (4.0)	34.7 (6)	159 (14)*

Results as mean (SD).
Dose of levodopa 160 ± 20 mg.
**p* < 0.05.

The results indicate that MDL 72.974 A potentiates the effects of individual doses of levodopa. Due to its prolonged symptomatic action the drug may improve motor fluctuations and improve night-time and early morning akinesia in patients with Parkinson's disease. Whether this potent and selective inhibitor of MAO-B reduces the progression of the underlying Parkinsonism by protective mechanisms² is still to be investigated.

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Sensorimotor syndrome relates to lacunar rather than to non-lacunar cerebral infarction

In a recent study in this journal, Landi *et al*¹ found similar clinical and CT scan features in patients with sensorimotor and those with lacunar stroke, as opposed to non-lacunar stroke patients. Their data favour the view that sensorimotor stroke is commonly due to lacunar infarction.

Prompted by this study we compared stroke patients with sensorimotor syndrome (N = 47) with those with other lacunar syndromes (pure motor, pure sensory, dysar-

thria-clumsy hand, and ataxic hemiparesis syndrome) (N = 99), and also with a group of patients with a cortical syndrome (N = 214), who were registered in a prospective database of all patients with a first, supratentorial brain infarct, as described elsewhere.² At the time of this analysis 374 patients were registered. Thirteen patients with a cause other than atherosclerotic cardiac or thromboembolism, and one with unknown initial stroke syndrome were excluded. For definitions and diagnostic criteria of the different stroke subgroups, we refer to a previous report.² Isolated monoparesis was taken as a cortical syndrome because it is generally caused by superficial infarction.³ Striatocapsular infarcts were classified as "cortical" because they resemble such infarcts with their clinical presentation and pathogenesis.⁴ We compared the frequency of both potential cardiac and carotid (> 50% diameter reduction on non-invasive testing) sources of embolism between sensorimotor syndrome and both lacunar and cortical syndromes. We studied the number of patients with severe initial handicap (a score of 5 on the Rankin scale) and the one month case fatality rate, and the frequency of lacunar and non-lacunar infarcts on CT scan.

All except 11 cortical syndrome patients had at least one CT. Forty three of the sensorimotor syndrome, 81 of the other lacunar syndrome group, and 139 of the cortical syndrome patients had non-invasive carotid testing.

The results are shown in the table. Differences were analysed by means of odds ratios (OR) with (Yates' corrected) 95% confidence interval (CI); differences in age were compared by two tailed Mann-Whitney U test.

Patients with sensorimotor syndrome had similar age distribution as those with lacunar syndrome, whereas they differed from those with cortical syndrome, who were older. The frequencies of both potential cardiac and carotid embolic source were equally low in sensorimotor and lacunar syndromes, but higher in cortical syndrome, suggesting that sensorimotor like lacunar syndrome^{2,5} most likely result from small vessel disease rather than from cardiac or carotid embolism. Sensorimotor syndrome resembled lacunar syndrome in a low number of severe strokes, a low early one month case fatality rate, and a low number of non-lacunar (mostly involving the cortex) infarcts on CT, whereas they differed significantly from cortical syndrome. There were no differences between the sensorimotor syndrome patients with, and those

without a CT lesion. The group with a lesion contained more cases with a potential cardioembolic stroke cause, and also with a Rankin score of 5, than those without a lesion. These differences were not statistically significant but do not suggest that sensorimotor syndrome without a CT lesion would be more likely to resemble cortical syndrome. Our results agree with those of Landi *et al*¹ and suggest that sensorimotor syndrome should be regarded as a lacunar syndrome, which means that it usually results from lacunar infarction due to cerebral small vessel disease, rather than non-lacunar infarction due to cardiac or carotid embolism. This conclusion is particularly important in patients with normal CT scans, for whom extensive cardiac investigation and angiography aimed at detecting operable carotid lesions are of dubious value, as with a CT proven lacunar infarct.² Taking accurate patient histories and performing a neurological examination, to differentiate between lacunar and cortical stroke syndrome therefore remain important in determining management options.

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Table Features of patients with sensorimotor syndrome compared with lacunar syndrome patients and cortical syndrome patients

	Sensorimotor syndrome N (%)	Lacunar syndrome N (%)	OR 95%CI	p-value	Cortical syndrome N (%)	OR 95%CI	p-value (two-tailed)
Number	47	99			214		
Male/female	22/25	58/41		NS	115/99		NS
Mean age (SD)	65.9 (10.4)	67.3 (11.7)		NS	72.4 (11.8)		<0.01
Cardiac embolism	6 (13)	9 (9)	1.46 (0.22-9.84)	NS	80 (37)	0.25 (0.10-0.60)	<0.01
Carotid sten >50%	1 (2)	12 (15)	0.14 (0.02-1.12)	NS	46 (33)	0.05 (0.01-0.23)	<0.001
Rankin score 5	6 (13)	10 (10)	1.30 (0.10-17.79)	NS	94 (29)	0.19 (0.08-0.44)	<0.001
30-day mortality	2 (2)	1 (1)	2.13 (0.02-43.12)	NS	34 (16)	0.12 (0.02-0.74)	<0.02
Lacunar infarct on CT	20 (43)	51 (52)	0.70 (0.30-1.63)	NS	19 (9)	3.27 (1.48-7.26)	<0.001
Non-lacunar infarct on CT	5 (11)	18 (18)	0.54 (0.14-2.01)	NS	145 (71)	0.05 (0.02-0.11)	<0.0001