

Matters arising

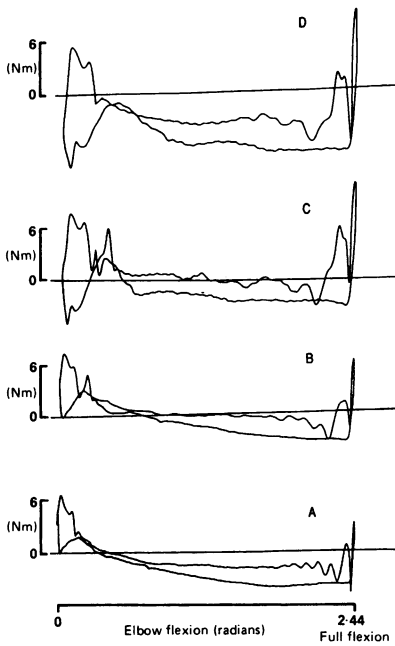


Fig 1 Length-tension plots of torque versus elbow flexion at 1.57, 2.09, 2.62 and 3.89 radians/s (A to D respectively) in a 46 year old healthy subject. Passive movements were continuous and oscillatory in which both extension and flexion were at the same velocity.

sitive effects are the viscous forces as shown here in a 46 year old subject (fig 1) and can be represented by the progression in force-velocity areas (fig 2). We have found in an environment where acceleration is known and velocity is controlled during the motion, a highly linear increase in area with respect to velocity. And this effect is reproducible. It

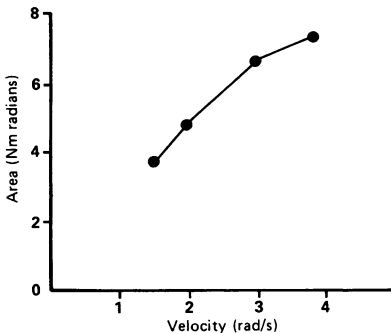


Fig 2 The relationship between the areas inscribed within the length-tension loop and the velocities of the passive movement.

seems unreasonable to attribute the neural or reflex effect seen in the added force levels above 120°/s to changes in elasticity. This normal linear function ( $r = 0.99$ ) from 90–220°/s represents a progression that includes the lumping of visco-elastic and inertial effects. But because limb mass and moment of inertia do not change, gravity correction is not necessary and qualitative statements can be made about the resistance to passive movements. This relationship is supported by earlier work in which a consistent linear relationship was found between reflex EMG and the velocity of stretch in the biceps over a wide range of velocities (0–500°/s).<sup>9</sup>

**Advantages of this approach.** Limiting measurement interval and overall time for patient assessment has been shown to be critical.<sup>10</sup> This procedure requires one sitting for a period of about 10 minutes. Predominately elastic changes can be estimated at velocities below reflex threshold, and as velocity is increased, the velocity threshold for reflex EMG can be detected. Since short term EMG events do not correlate well with torque output, the added viscous effects caused by heightened neural reflexes will alter the slope of area vs. velocity relationship from a straight line function when a velocity threshold is present.

**Disadvantages.** As yet we do not have a way to subtract the area's due to inertial effects without an estimate of the centre of gravity of the extremity.<sup>11</sup> The patient's tolerance of higher velocities of oscillating motion is less than linear motion at the same velocities. It is also harder for the patient to relax. These combined effects cause the measurement error to increase when compared to linear movement.

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References

- 1 Burke D. Spasticity as an adaptation to pyramidal tract injury. *Adv Neurol* 1988;47:401–23.
- 2 Lakie M, Tesementzu ST, Walsh EG, Wright G. Anaesthesia does not (and cannot) reduce muscle tone? *J Physiol (London)* 301:23P.
- 3 Wiegner AW, Watts RL Elastic properties of muscle measured at the elbow in man: I. normal controls. *J Neurol Neurosurg Psychiatry* 1986;49:1171–6.
- 4 Watts RL, Wiegner AW, Young RR. Elastic properties of muscle measured at the elbow in man: II. patients with Parkinsonian

rigidity. *J Neurol Neurosurg Psychiatry* 1986;49:1177–81.

- 5 Hayes KC, Hatze H. Passive visco-elastic properties of the structures spanning the human elbow joint. *Eur J Appl Physiol* 1977;37:265–74.
- 6 Young RR, Wiegner AW. Spasticity. *Clin Orthop* 1987;219:50–62.
- 7 Farrell M, Richards JG. Analysis of the reliability and validity of the communicator exercise device. *Med Sci Sports Exerc* 1986;18:44–9.
- 8 Hill AV. *First and Last Experiments in Muscle Mechanics*. Cambridge: Cambridge Univ. Press, 1970:27.
- 9 Ashby P, Burke D. Stretch reflexes in the upper limb of spastic man. *J Neurol Neurosurg Psychiatry* 1971;34:765–71.
- 10 Webster DD. The dynamic quantification of spasticity with automated integrals of passive motion resistance. *Clin Pharmacol Ther* 1964;5:900–8.
- 11 Allum JHJ, Mauritz KH. Compensation for intrinsic muscle stiffness by short-latency reflexes in human triceps surae muscles. *J Neurophysiol* 1984;52:797–818.

**Blood brain barrier permeability in multiple sclerosis using labelled DTPA with PET, CT and MRI**

Sir: Pozzili *et al* recently reported on the measurement of blood brain barrier (BBB) permeability in multiple sclerosis (MS) using 68-Ga-EDTA and positron emission tomography (PET).<sup>1</sup> Their paper, however, contains some numerical inconsistencies and in addition the permeability measured is much smaller than that indicated by our MRI studies for the reasons discussed below.

In their summary the authors quote a blood to brain influx constant  $K_i$  for Gallium-EDTA of 12.5 ml g<sup>-1</sup> min<sup>-1</sup> in multiple sclerosis patients with a clinical exacerbation of their disease, and a  $K_i$  of 3.2 ml g<sup>-1</sup> min<sup>-1</sup> for normal tissue. The measurements of multiple sclerosis were made in areas of the brain judged abnormal by high volume delayed CT scanning (HVD-CT). These values are clearly too high and contradict their table 3 which shows  $K_i = 12.5 \times 10^{-4}$  ml g<sup>-1</sup> min<sup>-1</sup> for multiple sclerosis patients and  $3.2 \times 10^{-4}$  ml g<sup>-1</sup> min<sup>-1</sup> for normal controls. Tables 3 and 4 also show for normal and multiple sclerosis brain the plasma volume ( $V_p$ ) in the range 3.3–4.5 ml g<sup>-1</sup>. These values are clearly impossible since even pure blood contains only about 0.55 ml g<sup>-1</sup> of plasma, and normal white matter only about 0.02 ml g<sup>-1</sup> of blood.<sup>2</sup>

The authors found BBB permeability in

the multiple sclerosis lesion increased only by a factor of 4 from normal. This contrasts with our MR findings using Gd-DTPA, in which signal enhancement is high (approximately 100%) in enhancing lesions, and negligible (<3%) in normal white matter.<sup>3</sup> These MR findings suggest that the BBB permeability is enhanced by at least a factor of 30 in active multiple sclerosis. At 45 minutes after contrast injection MRI shows uniform enhancement, like HVD-CT.<sup>4</sup> However, at shorter times (5–10 minutes) ring enhancement is usually seen in lesions >5 mm in diameter,<sup>4</sup> which is consistent with pathological descriptions of active inflammation and demyelination at the perimeter of multiple sclerosis plaques.<sup>5</sup> Later enhancement in the older, inner core of the lesion is probably caused by diffusion inwards from the ring enhancing edge. Using the CT scan to delineate the region of interest on the PET scan will produce a mean  $K_1$  over the whole lesion, thus significantly underestimating the  $K_1$  of the active ring-like part with defective BBB. The true  $K_1$  will be greater by approximately the ratio of total lesion area to ring area, that is, as much as twenty times higher. Even if the correct region of interest was used, PET is intrinsically incapable of resolving the ring enhancement in multiple sclerosis because its spatial resolution is too poor (9 mm in the plane of a 16 mm thick slice). Our preliminary measurements of  $K_1$  in the active part of the lesion using dynamic MRI scanning suggest values of  $K_1$  in the range 0.012–0.06 ml g<sup>-1</sup>min<sup>-1</sup> (3 lesions) that is 10–50 times higher than in the authors' table 3.

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## References

- 1 Pozzilli C, Bernardi S, Mansi L, *et al*. Quantitative assessment of blood-brain barrier permeability in multiple sclerosis using 68-Ga-EDTA and positron emission tomography. *J Neurol Neurosurg Psychiatry* 1988; 51:1058–62.

- 2 Leenders KL, Bearney RP, Brooks DJ. The effects of dexamethasone in brain tumour patients measured with positron emission tomography. In: Hartmann A, Hoyer S, eds. *Cerebral Blood Flow and Metabolism Measurement*. Berlin: Springer Verlag, 1985:465–70.
- 3 Miller DH, Rudge P, Johnson G, *et al*. Serial gadolinium enhanced magnetic resonance imaging in multiple sclerosis. *Brain* 1988; 111:927–39.
- 4 Kermode AG, Tofts PS, MacManus DG, *et al*. The early lesion of multiple sclerosis. *Lancet* 1988;ii:1203–4.
- 5 Prineas JW, Connell F. The fine structure of chronically active multiple sclerosis plaques. *Neurology* 1988;28:68–75.

## Pozzilli *et al* reply:

We are grateful to Drs Tofts and Kermode for giving us the opportunity to rectify a typographical omission in our article. In tables 2 and 3 the  $V_p$  should have been multiplied by  $10^{-2}$ , as correctly shown in our previous paper,<sup>1</sup> and in the summary the values of  $K_1$  are  $\times 10^{-4}$ . Clearly this omission solves a contradiction which is only too apparent. The values of  $V_p$  in the range of  $3.3\text{--}4.5 \times 10^{-2}$  ml g<sup>-1</sup> are in agreement with the values of CBV reported in the literature.<sup>2,3</sup>

Drs Tofts and Kermode, on the basis of signal enhancement, reach the conclusion that BBB permeability should be increased by a factor of 30 in active multiple sclerosis. This, according to them is in contrast with the increase by a factor of four reported by us. We frankly have some difficulty in comparing the two sets of data since one originates from a signal enhancement ratio and the other from a numerical value of  $K_1$  calculated on the basis of a kinetic model for the passage of substances across the BBB.<sup>1</sup>

Unfortunately we are unable to comment on the value of  $K_1$  measured with MRI since the underlying assumptions and the mathematical formulation of the method are neither reported in the letter, nor in the quoted reference. It should be pointed out, however, that  $K_1$  approaches in magnitude the permeability-surface area product (PS) only when  $PS \ll F$  (where  $F$  = blood flow).<sup>4</sup> Values of  $K_1$  as high as 0.06 ml g<sup>-1</sup>min<sup>-1</sup> would suggest that PS approaches  $F$  in magnitude. In these circumstances  $K_1$  is not only expression of PS, but would also depend upon blood flow. Thus for a correct evaluation of PS a measurement of local blood flow would be required.

Finally, our recent experience on Gd-DTPA suggest that ring enhancement in patients with multiple sclerosis is an uncommon finding. Moreover, none of the patients reported in our study showed a ring en-

hancement in the high volume delayed (HVD) CT scan.

## References

- 1 Iannotti F, Fieschi C, Alfano B, *et al*. Simplified and non-invasive PET measurement of blood-brain barrier permeability. *J Comput Assist Tomogr* 1987;11:390–7.
- 2 Leenders KL, Bearney RP, Brooks DJ. The effects of dexamethasone in brain tumour patients measured with positron emission tomography. In: Hartmann A, Hoyer S, eds. *Cerebral Blood Flow and Metabolism Measurement*. Berlin: Springer Verlag, 1985:465–70.
- 3 Pozzilli C, Itoh M, Matsuzawa T, *et al*. Positron emission tomography in minor ischemic stroke using oxygen-15 steady-state technique. *J Cereb Blood Flow Metab* 1987; 7:137–42.
- 4 Fenstermacher JD, Blasberg RG, Patlak CS. Methods for quantifying the transport of drugs across brain barrier systems. *Pharmacol Ther* 1981;14:217–48.

## Encephalopathy, deafness and blindness in young women: a distinct retinocochleocerebellar arteriopathy?

Sir: The recent paper by Bogousslavsky *et al*<sup>1</sup> documenting three patients who developed progressive neuropsychiatric and neurological disturbances with hearing and multifocal retinal artery branch occlusions, requires some comment.

Their first patient demonstrated an abnormality of the T-helper/suppressor cells in blood suggesting an immunological disturbance. This patient also showed elevations of the CSF protein and erythrocyte sedimentation rate. Their third patient, in addition to an elevated ESR of 27 mm/hour, also demonstrated positive antinuclear antibodies (1:320) as well as positive rheumatoid factor (1:160), and low complement levels were later also discovered.

We would draw attention to the recently defined "primary" antiphospholipid syndrome.<sup>2</sup> These patients may develop multiple infarct dementia,<sup>3</sup> and vascular occlusions occur, involving both venous and arterial circulations. Indeed there appears to be a strong association between the retinal vasculopathy described and the presence of CNS disease.<sup>4,5</sup> As many as 40% of these patients may be ANA negative, and there is only a 60%–70% concordance between "lupus anticoagulant" activity and the presence of anticardiolipin antibodies (aCL). The VDRL may only be positive in 20%–30% of patients. Other immunological dis-