

Matters arising

Sir: In a recent study of elderly subjects (*J Neurol Neurosurg Psychiatry* 1983; 46:410-3) Aziz, Leeming and Blair found a significantly lower mean plasma total biopterin in 18 patients with senile dementia of Alzheimer type than in 35 hospital patients (15 confused, 20 without confusion), 13 healthy controls and 17 schizophrenic patients. They suggest that the differences are due to reduced biopterin synthesis in the patients with Alzheimer's disease, a conclusion which, if correct, could be of considerable importance to the direction of future studies of the disease. Before accepting this explanation other possible explanations for their findings must be considered and investigated.

This group of workers have themselves shown that plasma total biopterin values are closely and positively related to plasma phenylalanine concentrations¹ and to renal function.² Plasma phenylalanine rises and falls with changes of phenylalanine intake and liver function. It is possible that differences between the groups in plasma phenylalanine and/or renal function could account for the differences in plasma biopterins recorded by Aziz *et al.* A few controls with impaired renal or liver function, and patients with dementia on a particularly low protein intake, could account for their findings. The way to deal with this difficulty is to measure plasma phenylalanine and creatinine at the same time as plasma total biopterin. This might also reveal that patients with Alzheimer's disease have increased plasma phenylalanines as well as low biopterins thus adding further weight to the authors' conclusions.

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Blair and Leeming reply:

Dr Smith draws attention to the changes in plasma total biopterins which correlate closely with changes in plasma phenylalanine concentrations.¹ She suggests that the lower mean plasma total biopterins in the eighteen patients with senile dementia could be due to reduced plasma phenylalanine levels or renal changes. We have previously reported that in senile dementia patients (six) with significantly lower fasting plasma biopterins than controls (five) (1.15 ± 0.14 (SE) versus $1.78 \pm 0.07 \mu\text{g l}^{-1}$; $p < 0.02$) the plasma phenylalanine fasting levels in the demented are significantly higher than in the controls (0.099 ± 0.003 (SE) versus $0.051 \pm 0.004 \text{ mmol. l}^{-1}$; $p < 0.001$) as is the P/T ratio ($1.9 \text{ v } 0.96$).^{2,3} An oral dose of 7 g of phenylalanine to these six demented patients produced significantly higher levels of plasma phenylalanine at 1, 2 or 3 hours following the dose than in control subjects and total plasma biopterin levels were similar in the demented patients to controls at 1 and 2, 3 and 4 hours following the phenylalanine dose.² These observations are consistent with the slow metabolism of phenylalanine due to reduced synthesis of tetrahydrobiopterin. Decreased renal clearance, a likely occurrence in the elderly, causes a significant increase in the plasma total biopterins.³ Clearly the reduced total plasma biopterin in senile dementia is not caused by low phenylalanine levels nor by renal insufficiency. Reference 2⁴ quoted by Dr Smith has no comment on renal function.

Another report has shown the plasma biopterin levels but not plasma neopterin levels are significantly reduced in Alzheimer's disease.⁵ This again suggests that a decrease in biopterin synthesis is found in Alzheimer's disease and the reduced levels are not due to altered kidney or liver function.

Direct measurement on necropsy human temporal lobe samples has now shown that tetrahydrobiopterin synthesis is significantly reduced in Alzheimer disease patients compared to controls.⁶

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Focal Paroxysmal Kinesigenic Choreoathetosis

Sir: I was interested to read Plant's report¹ of three patients in whom unilateral movements of paroxysmal kinesigenic choreoathetosis were focally induced by movement of the ipsilateral, but not the contralateral limbs. I have recently seen a 40-year-old woman with unilateral paroxysmal involuntary movements that could be precipitated by voluntary movement of either limb. This patient gave an 18 year history of periodic right-sided involuntary movements made up of finger clenching, wrist and elbow flexion with adduction of the arm drawing the fist across the chest. Occasionally the right side of the face would pull at the same time. There was no associated sensory aura. The movements would last less than a minute and when not experiencing the dyskinesia she had no neurological complaints. Initially these movements occurred only once every two months, always when lying down in bed at night. For the past four years they have occurred up to ten times per day and are frequently precipitated by use of the right limb. Family history was negative.

On examination with the arms outstretched there was a slight dystonic flexion of the fifth finger on the right side and on performing rapid alternating movements of the right hand the right foot took on a dorsiflexed and inverted posture which could not be precipitated by movement of the left hand. Carrying out fine finger movements of the right hand frequently precipitated a tremulous movement in the hand which would then progress to a clenching of the fingers and the full tonic posturing of the limb as described above. Each episode would last between 10 and

30 seconds. On several occasions it was impossible to precipitate the involuntary movements by persistent thumb to finger movements on the right hand; however, on relaxing the right limb and taking up a similar manoeuvre with the left, the right would immediately develop the involuntary movements as described. Passive movement did not precipitate an attack, nor did voluntary movement of either leg.

This woman demonstrated unilateral paroxysmal kinesigenic dystonic movements only. This dyskinesia was most commonly precipitated by voluntary movement of the affected limb; however, unlike those cases reported by Plant,¹ it was also possible to evoke similar attacks by voluntary movement of the contralateral hand. This suggests that whatever the specific precipitant of the dyskinesia, whether it be the movement itself or the anticipation of movement² it does not have to be limited to the limb affected by the choreoathetosis.

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Plant replies:

Dr Lang's interesting comments raise two important issues. The first concerns the nosology of the paroxysmal dystonias. The case described demonstrates features indicating that this may not be the same disorder as that first clearly distinguished from the other paroxysmal dystonias by Kertesz.¹ In particular most reported cases are normal on examination between attacks and also the frequent occurrence of attacks when not moving—particularly when lying in bed—would be most unusual. I would also suggest that certain features reported in most cases of paroxysmal kinesigenic choreoathetosis are likely to prove distinctive of a specific disorder. These are the importance of the abruptness of movements which precipitate attacks, the importance of prior inactivity and the occurrence of a refractory period following attacks. It is not clear from Dr Lang's account

whether these characteristic attributes were present.

The second issue concerns the importance of detailed analysis in cases of dystonia in which involuntary movements are induced by various stimuli. Such disorders are of potential importance in understanding the pathophysiology of dystonia and if others follow Dr Lang's example of careful observation a clearer picture may emerge from what is currently something of a can of worms.

As for Dr Lang's specific point I agree that the less rigidly linked focal activity and focal attacks are, then the more likely it is that a mechanism related to the initiation of movement is the primary precipitant rather than the motor activity *per se* or feedback from the limbs. I have observed a large number of attacks in cases 1 and 2 described in my article² and although I have never seen an attack in the contralateral limbs induced by hopping I have witnessed, in case 2, attacks provoked apparently by the anticipation of movement where no movement took place other than the attack itself. In the act of hopping all four limbs are moved: it was my intention to point out the importance of either the initial component of a complex movement or, conceivably, the side of the body to which attention is directed in determining the laterality of the attacks in my cases.

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Indomethacin-responsive episodic cluster headache

Sir: Since more attention has been paid to cluster headache various other forms of this disease have been distinguished besides its classic or episodic form.^{1,2} The localisation of the pain is the basis of the definition of this disease while the frequency and character of attacks take various forms.³ Apart from the classical types, we can also distinguish so-called transitional forms.^{4,5} The interesting description of the case presented by Geaney⁶ can not, I think, be classified as the episodic form, but is the transitional form between the episodic and the CPH forms. The effectiveness of indomethacin in cases of CPH is

regarded as one of the criteria for diagnosis. However, I would like to point out that indomethacin is also effective in transitional forms of cluster headache. In 1976 I described a case which was transitional between the chronic and the CPH forms. She was a 50-year-old woman who suffered from classic migraine in her childhood. When she was 45 yr she started to suffer from the episodic form of cluster headache, which then turned into the secondarily chronic one. After 2 years, during which the patient reported 1-3 attacks per day, exacerbation of the disease occurred when the number of attacks per day increased to 7 with simultaneous shortening of duration. When she was treated with indomethacin the attacks ceased completely after a few days. My case and the one presented by Geaney are not the only atypical forms of this disease, but it should be noted that indomethacin often proves to be effective when attacks are frequent.

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Geaney replies:

Chronic paroxysmal hemicrania (CPH) was reviewed in 1980¹ and it was apparent that prior to the development of the chronic stage, in which multiple attacks occur every day, there is frequently a preliminary stage during which the headache may occur in episodic or cyclical form (pre-CPH stage). This episodic stage has lasted for up to 19 years before evolving into the chronic stage.