shown no benefit after oral immunosuppression. Indeed, introduction of a moderately high dose of prednisolone caused a dramatic deterioration, a response that is recognised in CIDP.^{3,6} Unlike the modest clinical benefit seen by others after the administration of IVIg,⁷ our patient remains exquisitely sensitive to IVIg.

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Sodium valproate for tinnitus

In 1935 Barany serendipitously discovered the temporary relief of tinnitus after lignocaine injection of nasal turbinates.¹ Since that time, other agents known to suppress the activity of excitable membranes have been tried, including antiarrhythmic and anti-convulsant drugs. Among such drugs, carbamazepine has the best documented efficacy in patients with a positive lignocaine test,² but is generally unhelpful in unselected tinnitus populations and often discontinued due to adverse effects.^{2,3}

A 53 year old man with viral cardiomyopathy developed severe (60 dB) tinnitus after bilateral temporal lobe strokes. Various treatments including masking and diazepam were unhelpful. Carbamazepine (200 mg nightly) was effective, but was withdrawn due to progressive hyponatraemia (120 mM after two weeks of therapy), followed by the rapid recurrence of tinnitus. Sodium valproate (200 mg twice daily) was also promptly effective in suppressing tinnitus, and was well tolerated until his death due to cardiac arrhythmia one month later.

In part due to its diverse aetiology, pharmacotherapy of tinnitus has met with very limited success.^{2,4} Uncontrolled trials in the French³ and Japanese⁵ literature have indicated benefit from sodium valproate in selected patients, but its use seems not to have been described in English apart from a specialist monograph.² Tinnitus loudness⁵ and sensorineural pathology³ but not lignocaine response² seem to predict response. Valproate may also differ from carbamazepine in that it seems better tolerated in an unselected tinnitus population.³ Con-

trolled studies of valproate for this common, often debilitating⁴ condition seem warranted.

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Audible carotid dissection

Carotid dissection is a common cause of stroke in the young patient and can present with various clinical syndromes or symptoms. These may include stroke or transient ischaemic attack,¹ ipsilateral ptosis, isolated or multiple cranial nerve palsies,² carotidynia, hemicrania,³ scintillating scotomata, pulsatile tinnitus, or subjective bruit.⁴ I recently cared for a man who experienced an audible "creaking" sound heard even by his wife in the hours before a right middle carotid artery (MCA) infarct secondary to a carotid dissection. I think that this sound represented the actual dissection.

A forty three year old, right handed lawyer with a presumed viral pharyngitis and severe cough for two weeks duration returned from work at 6 00 pm and began hearing periodic, high frequency, "creaking" sounds in his right ear. These sounds occurred every 1-2 hours lasting a few seconds each time. These sounds were not pulsatile or rhythmic. He had not experienced these sounds previously with his illness. When sitting at the dinner table, his wife too heard these peculiar sounds. On admission she provided a detailed description of these sounds as the patient himself was lethargic. At midnight, he experienced a scintillating scotomata with right retroorbital headache and by 1 30 am was lethargic with a left sided weakness. According to the wife and the patient these sounds had now ceased and did not recur.

On examination he had diminished attention, and mental status was otherwise normal. Neck auscultation was normal and there was no audible creaking sound. Fundi and visual fields were normal. A left lower facial droop was present with otherwise normal cranial nerve function. Left arm plegia and left leg paresis was present with associated hyperreflexia and extensor plantar response. He reported diminished sensation to pin, position, and light touch and extinguished left sided touch on simultaneous bilateral stimulation. Brain MRI at 12 hours showed a T1 hypointense and T2 hyperintense lesion in the anterior MCA distribution, thrombus in the MCA (M-1 segment), with a suggestion of focal narrowing in the upper cervical region of the right internal carotid on MRA. An angiogram confirmed a right internal carotid dissection and MCA thrombus. The patient was anticoagulated and with rehabilitation is ambulatory with partial use of his left arm.

Whereas the clinical picture may be typical of carotid dissection, the clearly audible creaking sound that occurred in the early phase of the illness was unusual. I excluded relating this sound to middle ear congestion, hallucinosis, or aura of migraine or epilepsy as these possibilities would have been subjective phenomena not experienced by the patient's spouse. More commonly, auditory symptoms associated with carotid or vertebral dissection are related to altered vascular haemodynamics. Subjective sudden onset of bruit and pulsatile tinnitus are well described and are relatively frequent symptoms of carotid dissection. When present, these symptoms are constant, occasionally appreciated by auscultation, and usually persist even after presentation to the physician. Again however, to my knowledge they have not been reported as being heard externally. Aortic dissection can have a variable presentation, but I have been unable to find evidence of externally heard sounds in this setting.⁵

I suggest that these audible creakings in the context of a later documented arterial dissection were more likely the early tearing sounds themselves of the carotid dissection evolving over several hours. Such sound could have been heard externally and would have represented a progressively enlarging mechanical tear of a high pressure arterial system. The fact that these sounds were intermittent and recurrent, of limited duration, and unassociated with complaints of bruit or tinnitus suggests that the dissection developed slowly with several short bursts of "mini-dissection" before the devastating stroke. This case offers additional evidence that some carotid dissections may have a time course that if recognised might be amenable to emergency intervention. If a patient reports audible creaking without a clear explanation, an evolving arterial dissection should be considered.

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Gynaecomastia in association with phenytoin and zonisamide in a patient having a CYP2C subfamily mutation

Anticonvulsant drugs can have various side effects on endocrine functions, such as impotence, hirsutism, infertility, and thyroid dysfunction. Gynaecomastia is caused by many types of drugs such as methylodopa, tricyclic antidepressant drugs, isoniazid, and spironolactone,¹ but there have been only a few reports of gynaecomastia caused by anticonvulsant drugs, including phenytoin² and zonisamide.³ We recently encountered a young man with partial seizures, who

genetically had a heterozygous mutation of both CYP2C9 and CYP2C19,⁴ normally responsible for biotransformation of phenytoin in the human liver microsomal P-450 system.⁵ He developed gynaecomastia after increasing the dose of phenytoin.

The patient was an 18 year old man with a diagnosis of left parietofrontal lobe epilepsy since the age of 2 years, until which time his developmental milestones were normal. He had complex partial seizures occurring at least once every day despite various anticonvulsant drugs of usually sufficient dose including clonazepam, phenytoin, and carbamazepine, and zonisamide since the age of 9 years, when he had an epilepsy surgery for a focal high intensity abnormality on T2 weighted MRI in the left parieto-occipital area. His seizures were not controlled. At the age of 18 years, the patient had chronic implantation of subdural electrodes for evaluating the intractable seizures, and based on the results of the invasive evaluation, he had focal resection in the left parietal and mesial parietofrontal areas. After surgery his seizures decreased in frequency to once every week, and became less severe, accompanied by loss of awareness in only a third. Before and after the surgery he was taking phenytoin (175 mg/day), carbamazepine (900 mg/day), and zonisamide (400 mg/day) giving blood concentrations of 14.3 mg/l, 7.9 mg/l, and 13.2 mg/l, respectively. Two months after surgery, partly because of sleep deprivation, the patient had a cluster of complex partial seizures, some resulting in secondary generalisation, occurring seven times in 90 minutes. After a total of 375 mg phenytoin was intravenously loaded, his seizures were well controlled. Subsequently the medication was maintained at phenytoin (190 mg/day), carbamazepine (1100 mg/day), and zonisamide (400 mg/day), and the steady state, basal blood concentrations of these anticonvulsant drugs were 16.6 mg/l, 5.2 mg/l, and 9.7 mg/l respectively.

About a month later, the patient noticed bilateral enlargement of his breasts associated with some tenderness restricted to the centre of the breast. The size was about 3 cm in diameter. No galactorrhea was seen. Blood concentrations of luteinising hormone, follicle stimulating hormone, prolactin, and oestradiol were all normal. His liver function was also within normal limits except for slight increases in γ -GTP. The patient had had moderate gingival hypertrophy and mild hypertrichosis. He was taking no medication other than the anticonvulsant drugs.

On rare occasions gynaecomastia has been reported in patients taking phenytoin, and in some of them it disappeared after stopping phenytoin.⁷ The mechanism as to how gynaecomastia is caused by this drug is uncertain. It was pointed out that some drugs interfere with testosterone synthesis as well as action by blocking the cytosol receptor of androgen in target tissues. It has been shown that liver enzyme inducing antiepileptic drugs such as carbamazepine and phenytoin are associated with increased concentrations of serum sex hormone binding globulin and decreased amounts of free androgen available in the tissue.⁶ However, as for most drugs causing gynaecomastia, its mechanism is not well defined.

The anticonvulsant drug zonisamide has been clinically available in Japan for patients with seizures since 1989, and it is reported that three patients (age ranging from 3 years to 32 years) taking zonisamide (60 to 600

mg/day) developed gynaecomastia from 10 days to 1 year after taking zonisamide, and in all of them it disappeared after stopping zonisamide.³ Therefore, in the present patient, it is possible that both phenytoin and zonisamide played important parts in the development of gynaecomastia. However, the patient had been on zonisamide for the past 8 years, and its dosage was not increased before gynaecomastia developed. On the other hand, after phenytoin was loaded when he had frequent seizures, its maintenance dosage increased. Therefore, phenytoin is most likely a causative agent. Adolescent gynaecomastia usually occurs bilaterally, although asymmetric, in many boys as a physiological type, often during puberty with a mean onset age of 14 years, and it is correlated with transiently raised oestradiol of unknown origin before completion of puberty.¹ However, there was no increase in oestradiol in the present patient.

The patient had a heterozygous point mutation in the defective allele of CYP2C9 and CYP2C19,⁴ and in such patients V_{max} values in the pharmacokinetics of phenytoin were 40% lower than those in patients with a normal type CYP2C subfamily (see subject No 43 in fig 1 of Odani *et al*) and thus our patient's maintenance dose of phenytoin (175 mg/day) was relatively small to achieve an appropriate blood concentration (14.3 mg/l). After having increased the maintenance dose of phenytoin by 15 mg/day, the blood concentration was kept <20 mg/l, and clinically he did not show toxic symptoms such as cerebellar ataxia and gaze evoked nystagmus. The presence of a heterozygous CYP2C subfamily mutation might have played some additional part either in developing this rare side effect or in facilitating physiological gynaecomastia of the adolescent type.

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Neuropsychological prediction of dementia in Parkinson's disease

Mahieux *et al*¹ report on an interesting study of predictors of dementia in Parkinson's disease. We have certain reservations about the results because of the methodological limitations of the study.

The diagnosis of dementia was made by retrospective case note review or retrospective completion of questionnaires including some by non-specialists which raises questions about the validity of diagnosis. The researchers making the diagnosis of dementia were not blind to neuropsychological test score, which raises the possibility of observer bias. The study was uncontrolled so that the estimate of the incidence of dementia cannot be adequately interpreted because it is not known what the incidence in the general population would be using this method of case identification.

The findings of predictors of dementia are a little puzzling. Although four variables are reported as predictors, this seems to be misleading because for all but one of these the 95% confidence interval for the relative risk includes the figure one, indicating that the relative risk is not significant at the 5% level using a hypothesis test.² The p values for two of these variables were indeed greater than 0.05, but although the p value is given for the WAIS picture completion subtest as 0.03 (table 3, not table 2 as stated), the 95% confidence interval for the relative risk includes one. If these two statistical tests give different answers, which is correct?

For only one predictor variable did the 95% confidence interval of the relative risk lie outside one. This variable, age at onset of Parkinson's disease, was entered into the multivariate model, but it seems that age at inception to the study was not entered into the model. It is well known that dementia in Parkinson's disease is associated with age.^{3,4} If age onset is correlated with age at entry to the study as has been found by others^{3,5} then age at onset of Parkinson's disease is confounded. Many studies have reported that dementia in Parkinson's disease is associated with older age at onset, but those studies which have controlled for the effect of age have not found such an association.^{5,6}

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