LETTERS TO THE EDITOR

Recurrent spontaneous accessory neuropathy

Isolated spinal accessory nerve palsy of obscure or spontaneous origin is an uncommon but well recognised entity.¹ We describe the first reported instance of recurrent spontaneous accessory palsy.

At the age of 23 the patient developed an aching discomfort in the right shoulder and neck. This resolved after a few days but after several weeks he became aware of weakness of shoulder elevation. Examination revealed weakness and wasting confined to the right trapezius muscle. Nerve conduction studies of the accessory nerve, recorded in the trapezius, revealed latencies of 4.3 ms on the right and 2.9 ms on the left (normal < 3.2 ms). Electromyography showed large motor unit potentials and reduced recruitment in the right trapezius only. After four to five months the condition improved and the size and strength of the right shoulder returned to normal.

He remained well and continued to work as a policeman until he was 31, when he again developed an ache in the right shoulder after exercising with five-pound dumb-bells. The ache persisted for two to three weeks but was never severe and did not interfere with his sleep. Naproxen provided some relief. About three weeks after the onset of pain, the patient began to notice wasting of his right shoulder and weakness of shoulder abduction. Two weeks later the pain had entirely resolved but he was now aware of the right shoulder hanging lower than the left. He had no sensory loss or pain other than in the shoulder. The other limbs and sphincter function remained normal.

Examination revealed a fit man with marked wasting of the right trapezius muscle and moderate weakness of shoulder elevation. There was right scapular winging of the trapezius type, which was present with the arm at rest and accentuated by lateral elevation of the arm. The right sternomastoid muscle was normal. No wasting or weakness was observed in the other right shoulder girdle muscles and the remaining cranial nerves and other limbs were normal. General examination was normal and there was no sign of injury or abnormality on the lateral side of the neck.

Cervical radiographs and myelography of the foramen magnum were normal. CT scan of the neck and skull base revealed no abnormality. The cerebrospinal fluid (CSF) was clear and colourless, with four lymphocytes and a protein of 0.34 g/l. Serum glucose, full blood count, sedimentation rate, C-reactive protein, antinuclear factor, and routine biochemistry were normal.

Nerve conduction studies of the accessory nerve, recording trapezius, revealed a considerably decreased amplitude of the compound muscle action potential on the right, but the distal latencies were similar and normal on both sides (right = 3.2 ms,

left = 3.1 ms). Electromyography revealed fibrillation potentials and large motor unit potentials with reduced recruitment in the right trapezius, and normal findings in the serratus anterior, infraspinatus, deltoid, biceps, brachioradialis and extensor digitorum communis.

Our patient experienced two similar episodes, separated by eight years, of shoulder ache followed by right trapezius weakness and wasting. On both occasions clinical and electromyographic examination found no abnormality except in the right trapezius, implying the presence of a lesion affecting the accessory nerve distal to the innervation of the sternomastoid. He appeared to make a complete recovery after the first episode, only to suffer a recurrence eight years later. Investigation has not shown an underlying cause and we therefore believe he is the first reported instance of a recurrent spontaneous accessory palsy. Although onset of the second episode coincided with light exercise with weights, these were small (5 pounds) and seem unlikely to have produced a stretch injury of the accessory nerve.²

Due to its complicated course, the accessory nerve may be damaged by a wide range of processes affecting the cervical spinal cord, spinal canal, jugular foramen and skull base, carotid sheath, or posterior triangle of the neck.³ The nerve is particularly vulnerable as it crosses the posterior triangle, where injury occurs most often following radical neck dissection or lymph node biopsy, resulting in weakness and wasting of the trapezius.

Spillane described three patients in 1949 who had clinical evidence of isolated accessory neuropathies, the cause of which was obscure.⁴ Follow up for some months showed no evidence of improvement of the weakness and atrophy of the sternomastoid and trapezius. Four similar cases were studied clinically and electrophysiologically by Eisen and Bertrand in 1972;¹ one of their patients recovered completely in 22 months, but two did not improve and one was lost to follow up. There have been occasional case reports of isolated "spontaneous" accessory palsy in the literature since then, but our case is the first in which there was recovery and spontaneous recurrence in the same nerve. Typically there is abrupt onset of pain in the lateral neck or shoulder of varying degrees of severity, which then subsides over several weeks and is followed by wasting and weakness of the trapezius and sternomastoid, or both. Recovery has occurred in a minority of the reported cases and takes several months to one or two years.

Analogies may be drawn between isolated spontaneous accessory palsy and two other more common entities, idiopathic facial (Bell's) palsy and neuralgic amyotrophy (Parsonage Turner syndrome). Common to all three conditions is pain at the outset, followed by muscle weakness and atrophy, which subsequently recovers to a variable extent. In their classical presentations, Bell's palsy and neuralgic amyotrophy are quite distinct entities, but occasionally cases incorporate elements of both. Neuralgic amyotrophy in particular is now being recognised as an increasingly diverse disorder,⁵ although accessory or other cranial neuropathies are rarely described as part of this syndrome. In our patient, the involvement of a single cranial nerve and relatively mild pain seems to us more akin to Bell's palsy than neuralgic amyotrophy and

recurrent idiopathic facial palsy is well recognised.⁶

The authors thank Professor J Newsom-Davis for his helpful discussions and Dr K Mills for performing the second electromyographic examination.

COLIN CHALK,
HYAM ISAACS*

Department of Clinical Neurology,
Radcliffe Infirmary,
Oxford, United Kingdom

Department of Physiology,*
Witwatersrand University Medical School,
Parktown, Republic of South Africa

- 1 Eisen A, Bertrand G. Isolated accessory nerve palsy of spontaneous origin. *Arch Neurol* 1972;27:496-502.
- 2 Logigian EL, McInnes JM, Berger AR, Busis NA, Lehigh JR, Shahani BT. Stretch-induced spinal accessory palsy. *Muscle and Nerve* 1988;11:146-50.
- 3 Pettrera JE, Trojaborg W. Conduction studies along the accessory nerve and follow-up of patients with accessory palsy. *J Neurol Neurosurg Psychiatry* 1984;47:630-6.
- 4 Spillane JD. Isolated unilateral spinal accessory nerve palsy of obscure origin. *Br Med J* 1949;2:365-6.
- 5 England PD, Sumner A. Neuralgic amyotrophy: an increasingly diverse entity. *Muscle Nerve* 1987;10:60-8.
- 6 Ekblom KA. Plicated tongue in Melkersson's syndrome and in paralysis of the facial nerve. *Acta Med Scand* 1950;138:42-7.

Pesticide toxicity and motor neuron disease

Pyrethrins are neurotoxins that kill insects by paralysis—"knock down". This is thought to be secondary to an effect on sodium channels in motor neurons. Mammals are spared from this effect as, unlike insects, they can metabolise pyrethrins in the hepatic microsomal system to non toxic compounds.¹

We previously reported a case simulating motor neuron disease (MND) closely associated with over-exposure to a pyrethrin and chlordane based insecticide.² The chlordane component is metabolised to various compounds (including oxychlordane and epoxychlordane) via the cytochrome P₄₅₀ enzyme system.^{2,3} However, pyrethrins such as permethrin are metabolised by different routes (fig). Following esterase cleavage, two products are formed which are further metabolised then eliminated. In mammals,^{3,4} metabolite A is excreted in the urine as a glucuronide conjugate. Metabolite B undergoes oxidation and hydroxylation to yield mainly C and D, with other compounds. Conjugates of minor metabolites with glycine,³ glutamic acid⁴ and taurine⁵ have been noted. However, the elimination of metabolites C and D in the rat is by sulphate conjugation³ which is the major metabolic pathway for permethrin.

This is of interest since we recently reported⁶ that MND patients have a defect in their ability to convert cysteine into inorganic sulphate and also show a poor capacity to form the sulphate conjugate of paracetamol. In the light of these observations, the 4'-Hydroxy-3-phenoxy benzyl alcohol (metabolite C) and/or 4'-Hydroxy-3-phenoxy benzoic acid (metabolite D) may be responsible for the neurotoxicity that resulted in our patient suffering from his MND-type illness. Some environmental chemicals generally

thought of as harmless may therefore be toxic to a small proportion of the population who have an inability to metabolise them easily to safer compounds.

G B STEVENTON
R H WARING
School of Biochemistry,
University of Birmingham,
Birmingham
A C WILLIAMS
Department of Clinical Neurology,
Queen Elizabeth Hospital,
Birmingham, United Kingdom.

- Casida JE, Gammon DW, Glickman AH, Lawrence LJ. Mechanisms of selective actions of pyrethroid insecticides. *Ann Rev Pharmacol Toxicol* 1983;23:413-38.
- Pall HS, Williams AC, Waring RH, Elias E. Motor Neurone Disease as manifestation of pesticide toxicity. *Lancet* 1987;ii:685.
- Hutson DH. The metabolic rate of synthetic pyrethroid insecticides in mammals. *Prog Drug Metab* 1979;3:215-52.
- Hathway DE. *Foreign compound metabolism in mammals*, vol 5. London: Chemical Society, 1979:156-8.
- Hutson DH, Casida JE. Taurine conjugation in metabolism of 3-phenoxybenzoic acid and the pyrethroid insecticide cypermethrin in mouse. *Xenobiotica* 1978;8:565-71.
- Steventon G, Waring RH, Williams AC, Pall HS, Adams D. Xenobiotic metabolism in motorneurone disease. *Lancet* 1988;ii:644-7.

(+)-PHNO: a new anti-Parkinsonian agent which does not induce chorea in MPTP-treated squirrel monkeys

Exciting advances in drug delivery technology to control fluctuations in response to anti-Parkinsonian therapy are under way.¹ One recent development is a rate-controlled transdermal delivery system for the selective

D₂ agonist (+)-PHNO which was capable of maintaining stable plasma levels in the therapeutic range throughout a 24 hour period in primates.² The suitability of (+)-PHNO for rate-controlled absorption through the skin sets it apart from conventional anti-Parkinsonian agents. However, as well as "on-off" swings, many Parkinsonian patients also have debilitating drug-induced dyskinesias, especially chorea.³ The pathophysiology of this side-effect is poorly understood. We now report that (+)-PHNO, unlike levodopa, does not induce chorea in MPTP-treated squirrel monkeys.

The subjects had previously served in experiments using transdermal application of (+)-PHNO² and had all received intermittent exposure to levodopa during the two years before this study (total exposure ranged from 70 to around 1500 mg/kg po for different animals). Locomotor activity and drug-induced choreoathetosis in each limb was scored continuously by direct observation every five minutes for up to three hours using a clinically-based rating scale of 0-4 according to frequency and severity. Dyskinesias in each limb were rated separately as follows: 0 = absent; 1 = occasional/mild; 2 = intermittent/moderate; 3 = frequent/marked; 4 = continuous/severe. Levodopa was administered by oral gavage at 5, 10, 15 or 20 mg/kg 1h following treatment with double the respective dose of carbidopa. (+)-PHNO was examined at 0.625, 1.25, 2.5 or 5 µg/kg sc in the leg.

Administration of levodopa caused a dose-dependent increase in locomotor activity accompanied by choreoathetoid movements affecting the limbs, especially the legs. These reached a peak some 40-60 minutes after treatment and were characterised by repetitive flexion/extension or circling movements of the hands, forearms, hindlegs and feet and gyration about the pelvis. Buccolingual dyskinesias were not observed. Choreo appeared less severe at the highest dose of levodopa (20 mg/kg) due to the emergence of verticalisation or climbing behaviour between 90 and 165 minutes after treatment. In contrast, treatment with (+)-PHNO induced marked locomotor stimulation, but no chorea was observed in the limbs at any dose examined (see table). Unlike levodopa, lashing movements of the tail were observed following treatment with (+)-PHNO; the relevance of these movements for dyskinesias in humans is not clear.

The absence of chorea in MPTP-treated squirrel monkeys following acute administration of the D₂-selective agonist (+)-PHNO agrees with a similar finding using chronic treatment with bromocriptine for five months in macaques.⁴ Similarly, in stage I-III Parkinsonian patients, Stoessl *et al*⁵ did not make any mention of dyskinesias following acute single dose oral treatment with (+)-PHNO. Interestingly, the less selective D₂ agonist apomorphine has been reported to reduce

chorea in Parkinsonian patients receiving levodopa therapy,⁶ in Huntington's disease⁷ and in neuroleptic-induced tardive dyskinesia.⁸ However, it should be noted that dyskinesias have occasionally been observed after administration of (+)-PHNO both in primates⁹ and in humans.¹⁰ The reason for this discrepancy is not known, but may be related to the severity of Parkinsonism, duration of prior treatment with levodopa ("priming"), and type of dyskinesia (chorea or dystonia).

Our findings, and those of others, clearly indicate a difference between the effects of a nonselective, indirect agonist (levodopa) and D₂-selective direct agonists in the genesis of chorea in the Parkinsonian brain. One interpretation of these findings is that stimulation of D₁ receptors may induce chorea. D₁ binding sites are particularly high in the medial pallidal segment,¹¹ an area implicated in the induction of chorea.¹² It is also of interest that the direct nigropallidal dopamine pathway is relatively unaffected by the neurotoxin MPTP,¹³ and this could provide a direct route for the production of chorea by levodopa.

We would predict that use of a directly acting selective D₂ agonist such as (+)-PHNO via a sustained release preparation in de novo Parkinsonian patients might greatly reduce the incidence of both chorea and motor fluctuations whilst giving effective relief from akinesia.

We are extremely grateful to Professor C D Marsden for his evaluation of the drug-induced dyskinesias induced by levodopa and (+)-PHNO.

N M J RUPNIAK
S BOYCE
M J STEVENTON
SD IVERSEN
Merck Sharp and Dohme Research Laboratories,
Neuroscience Research Centre, Terlings Park,
Harlow, Essex, CM20 2QR, United Kingdom

- Stahl SM, Wets KM. Recent advances in drug delivery technology for neurology. *Clin Neuropharmacol* 1988;11:1-17.
- Rupniak NMJ, Tye SJ, Jennings CA, *et al*. Therapeutic efficacy of a novel transdermal delivery system for (+)-PHNO in Parkinsonian squirrel monkeys. *J Neurol Neurosurg Psychiatry* 1989;52:289-90.
- Markham CH. The choreoathetoid movement disorder induced by levodopa. *Clin Pharmacol Therap* 1971;12:340-3.
- Bedard PJ, Di Paolo T, Falardeau P, Boucher R. Chronic treatment with L-DOPA, but not bromocriptine induces dyskinesia in MPTP-Parkinsonian monkeys. Correlation with ³H-spiroperone binding. *Brain Res* 1986;379:294-9.
- Stoessl AJ, Mak E, Calne DB. (+)-4-propyl-9-hydroxynaphthoxazine (PHNO), a new dopaminomimetic, in treatment of Parkinsonism. *Lancet* 1985;ii:1330-1.
- Duby SE, Cotzias GC, Papavasiliou PS, Lawrence WH. Injected apomorphine and orally administered levodopa in Parkinsonism. *Arch Neurol* 1972;27:474-80.
- Corsini GU, Onali PL, Masala C, Cianchetti C, Mangoni A, Gessa GL. Apomorphine hydrochloride-induced improvement in Huntington's chorea. *Arch Neurol* 1978;35:27-30.

Table Induction of locomotor activity and chorea following treatment with levodopa or (+)-PHNO in MPTP-treated squirrel monkeys

	Levodopa (mg/kg po)					(+)-PHNO (µg/kg sc)				
	Vehicle	5	10	15	20	Vehicle	0.625	1.25	2.5	5.0
	Score summed over 180 minutes					Score summed over 75 minutes				
Locomotor activity	9 (10)	21 (6)*	34 (6)*	45 (8)*	31 (5)*	14 (4)	24 (6)*	28 (3)*	35 (3)*	42 (2)*
Chorea	0	4 (2)	64 (20)*	188 (24)*	156 (28)*	0	0	0	1 (1)	0

Values are expressed as the mean (1 SEM) for data obtained using seven animals.

*p < 0.01 compared to vehicle treatment, Dunnett's multiple comparison test.