

## LETTERS TO THE EDITOR

### A case of pandysautonomia with associated sensory ganglionopathy

Since Young *et al*<sup>1</sup> described a patient with acute loss of sympathetic and parasympathetic functions in 1969, many similar cases have been reported as being acute idiopathic autonomic neuropathy.<sup>2</sup> Apart from acute cholinergic neuropathy, there are four types of acute idiopathic autonomic neuropathy, classified according to somatic nerve involvement: acute pandysautonomia, which has minimal or no motor or sensory dysfunctions<sup>3</sup>; acute autonomic and sensory neuropathy in which sensation is seriously involved<sup>4-6</sup>; Guillain-Barré syndrome with prominent dysautonomia, manifesting autonomic and somatic motor dysfunctions; and acute autonomic sensory and motor neuropathy, characterised by prominent dysautonomia and severe motor and sensory impairment. Despite minimal or no sensory disturbance, reduction of myelinated fibres in biopsied sural nerve has been found in several cases with acute pandysautonomia.<sup>3</sup> However, the exact site of pathological involvement in the sensory system remains unknown, because postmortem examinations have seldom been performed. We report a case of acute pandysautonomia with no evidence of significant somatic nerve involvement, accompanied by dorsal root ganglionopathy shown by postmortem examinations.

An 18 year old male student experienced low grade fever, vomiting, and tingling pain in the limbs on 26 February 1987. Orthostatic syncope occurred three times on the next day. Difficulty in emptying the bladder, alternate diarrhoea and constipation, and lack of sweating over the whole body developed rapidly. He was admitted to the Third Department of Internal Medicine, Medical College of Oita on 24 April 1987. On physical examination, he weighed 46 kg, with a recent weight loss of 14 kg. Blood pressure was 108/78 mm Hg in the supine position and heart rate was 88/min. When changing from the supine to the upright position, he lost consciousness and blood pressure became unmeasurable. On neurological examination, he had emotional instability. Both pupils were midsized, irregular, and reacted sluggishly to light. Jaw jerk was slightly exaggerated and deep tendon reflexes of the limbs were diminished. No obvious muscle weakness was found. Touch sensation and deep sensation were normal, but dysaesthesia and hypalgesia on his face and the upper part of the level of Th4, and slight hypalgesia of the limbs were found. The clinical manifestations of autonomic failure were orthostatic hypotension, lack of sweating, alternative diarrhoea and constipation, and impotence.

There were no abnormal findings in laboratory examination of blood and urine. Cell count in the CSF was normal, but protein concentration was slightly high at 54 mg/dl. Head CT and EEG were normal. Nerve conduction studies and EMG showed no abnormalities. Right sural nerve biopsy showed a marked loss of small myelinated and unmyelinated fibres. There were some

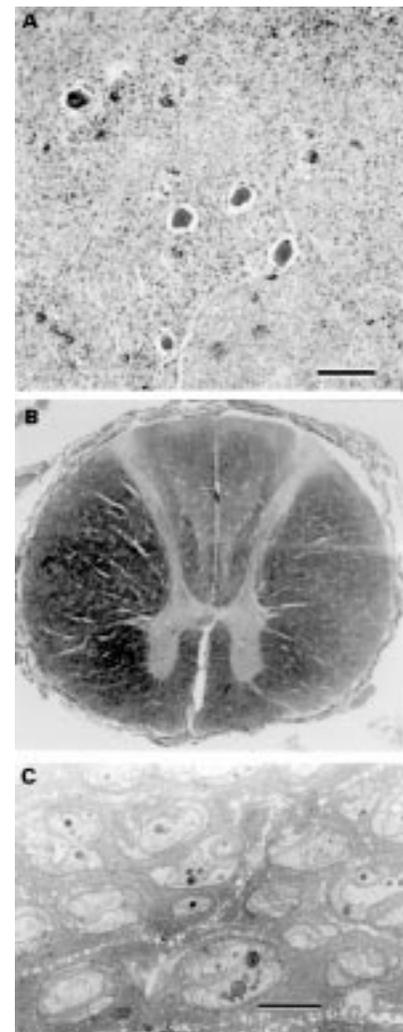
myelin ovoids in teased fibres. The hand grip test and the cold pressure test showed no rise in blood pressure. There was no overshoot in the Valsalva manoeuvre. Serum noradrenalin concentration decreased to 110 pg/ml (normal 145-575 pg/ml) at rest, and failed to respond to tilting. A noradrenalin infusion test (0.01-0.04 µg/kg/min) showed an excessive increase in blood pressure, from 90/58 to 120/78 mm Hg. The R-R interval variation was 4.55% at rest (normal 3%-6%). During ocular pressure test the patient had a normal bradycardic response. The instillation of 1.25% adrenaline into the conjunctival sac of the eye produced 37.5% dilatation of the pupil (normal <25%). Five per cent cocaine and 5% tyramine produced 12.5% and 28.6% dilatation respectively (normal; >30%). Addition of 2.5% methacholine resulted in a 12.5% reduction in pupillary size (normal <25%). Sympathetic skin responses were not evoked. Ameszium metilsulphate, an indirect sympathomimetic agent, was effective on orthostatic hypotension and coughing attacks. In April 1992, the patient fractured both legs in a traffic accident and was admitted to the Department of Orthopedics in Hiroshima University Hospital. On admission, he still complained of dizziness on standing, defective sweating, urinary bladder symptoms, and impotence. No sensory symptoms and signs were found. Nerve conduction studies were normal. The leg fractures were difficult to heal, and he underwent orthopaedic surgery several times. Although nerve conduction studies again disclosed no abnormality, he developed severe pneumonia and died of respiratory failure at the age of 25 in 1994.

On necropsy 10 hours after death, the brain weighed 1440 g, and no tumour was found in any part. The most prominent finding was located in the lumbar (L5) dorsal root ganglia. There was a marked reduction in the number of ganglionic neurons, whereas clusters of satellite cells were easily seen (figure A). The dorsal columns of the spinal cord showed a loss of myelinated fibres (figure B). No other detectable changes were present in the CNS including the brainstem, the intermediolateral nucleus of the thoracic spinal cord, and Onuf's nucleus. The celiac ganglia showed no abnormalities, but the sympathetic trunk was not examined. Lymphocytic infiltrates with perivascular distribution were not found anywhere in the nervous system. Electron microscopic examinations of the left distal sural nerve showed profound changes with a remarkable reduction in both myelinated and unmyelinated fibres, which decreased to 1236, and 4560/mm<sup>2</sup> /unit respectively. The size/frequency histogram of myelinated fibres showed a reduction in both large and small fibres. The histogram of axons devoid of myelin showed a monomodal curve with a peak situated at about 1.2 µm. Numerous budded Schwann cell bands were found (figure C), often associated with cells surrounded by additional layers of basement membrane. Myelin sheath irregularities were occasionally encountered. Regenerative alterations such as growth cones, clusters of small myelinated axons, and onion bulb formations were rarely seen.

The patient rapidly developed severe autonomic failure with only mild sensory nerve involvement manifested by dysesthesia and hypalgesia. Orthostatic hypotension and diminished sweating indicated sympathetic failure. Parasympathetic failure was assumed from alternate diarrhoea and constipation,

bladder paresis, and penile impotence. Abnormally decreased serum concentration of noradrenaline that remained low during tilting, and excessive increase in blood pressure by low concentration noradrenalin infusion suggested that the main lesion was located in the postganglionic fibres of the sympathetic system. This notion was consistent with the profound loss of unmyelinated fibres in the sural nerve. As no pathological alterations were found in the CNS except for the posterior columns of the spinal cord, we diagnosed this case as acute idiopathic autonomic neuropathy, based on the associated somatic sensory and motor neuropathy. The present case could be clinically regarded as acute pandysautonomia, as the patient's sensory symptom was mild and short lasting and because no abnormalities were found in nerve conduction studies.

The site of pathological involvement of the sensory system in patients with acute pandysautonomia has not been clarified. Our patient, as those in previous reports<sup>7</sup>, had a loss of myelinated fibres on sural nerve biopsy. Also, we found that the dorsal root ganglia showed a loss of ganglionic neurons and clusters of satellite cells. Only a few cases



(A) Loss of ganglionic neurons with clusters of satellite cells in the dorsal root ganglion. (Haematoxylin and eosin stain, bar = 100 µm.) (B) Loss of myelin staining in the dorsal columns of the thoracic spinal cord. (Luxol fast blue / Nissl stain). (C) Numerous budded Schwann cell bands in the sural nerve (bar = 2 µm).

of acute idiopathic autonomic neuropathy have been verified by necropsy<sup>4,5</sup>. Fagius *et al*<sup>6</sup> and Tohgi *et al*<sup>7</sup> found a marked loss of myelinated nerve fibres in the dorsal column, dorsal root, and peripheral nerve. Disappearance of nerve cell bodies replaced by clusters of satellite cells in the dorsal root ganglia was found in the patient of Fagius *et al*.<sup>4</sup> Stoll *et al*<sup>8</sup> also found symmetric degeneration of the dorsal columns with severe ganglionitis of both the sensory and autonomic ganglia. However, their patients showed a marked sensory disturbance with no evoked sensory nerve action potentials, as well as motor nerve involvement of a greater or lesser degree. Therefore, these cases could be classified as acute autonomic and sensory neuropathy or acute autonomic and sensory and motor neuropathy. Also, the patient of Fagius *et al*<sup>4</sup> had an associated malignant tumour in the testis that recurred during the course of pandysautonomia. Neuropathological examination disclosed CNS involvement manifested by degeneration in the preganglionic autonomic nervous system in the case of Tohgi *et al*,<sup>7</sup> and a mild chronic encephalomyelitis with perivascular lymphocytic infiltrates in the patient of Stoll *et al*.<sup>8</sup> The present case could be the first that showed sensory ganglionopathy associated with acute pandysautonomia.

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### Premenstrual exacerbations of multiple sclerosis

Although relapses of multiple sclerosis occur unpredictably and at odd intervals, two factors have been identified that may trigger an exacerbation: viral infections and the puerperium.<sup>1,2</sup> Viral infections probably act through a release of inflammatory cytokines, such as interferon- $\gamma$  (INF- $\gamma$ ), that stimulate the immune system and facilitate the entry of activated T lymphocytes into the CNS.<sup>1</sup> Relapses during the puerperium are likely to be precipitated by changes in the hormonal milieu after delivery.<sup>2</sup> We report on three patients with multiple sclerosis in whom successive exacerbations occurred exclusively during the premenstrual period.

Patient 1, a 21 year old women student sought evaluation for episodes of alternating right and left sided paraesthesias, which existed for about 4 months. She also complained of fatigue. There was a history of infectious mononucleosis 6 years earlier. She did not use an oral contraceptive. Neurological examination showed hyperreflexia and Babinski's sign in the right leg. Magnetic resonance imaging of the brain showed multiple white matter lesions on T2 weighted sequences, mainly in the left occipital and right parietal lobe. Oligoclonal bands were present in the CSF. One month later she was admitted to hospital because of weakness in the left leg, urge incontinence, and diminished sensation below Th7. Symptoms had started 3 days before her menstruation. She was treated with 1 g/day intravenous methylprednisolone for 5 days with rapid improvement over the next 2 weeks.

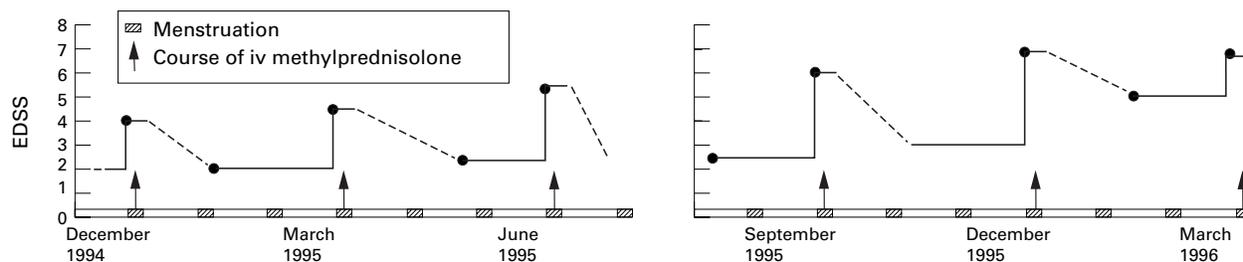
One month later she presented with a left hemiparesis and diminished sensation below Th1, which had started 2 days before the menstruation. She was treated with high dose intravenous methylprednisolone. During the next premenstrual period, 1 day before onset of the menstrual bleeding, she developed right sided cerebellar ataxia and diminished vision in the left eye; the expanded disability status scale (EDSS) was 5.0. She received a course of high dose intravenous methylprednisolone. Two months later the EDSS was 2.5, and she was included in an open pilot study with bromocriptine. Her clinical state did not change until 11 months later when she presented with worsening of right sided cerebellar ataxia; the symptoms had started 2 days before the menstruation. The ataxia improved gradually without corticosteroid treatment. After completion of the 1 year period specified in the trial protocol, she continued bromocriptine for another 8 months, and then stopped. She had no relapses on follow up for >3 years. At the last visit her EDSS was 2.0.

Patient 2 gave birth to two boys after uncomplicated pregnancies at the ages of 21 and 26. She used an oral contraceptive

between the ages of 28 and 31. At the age of 33, 2 days before her menstruation, she noticed weakness in the right leg. This improved gradually over the next 3 weeks. Six months later, on the day before her menstruation, she developed a right sided hemiparesis. Brain MRI showed widespread white matter lesions of high intensity signals on T2 weighted sequences. Visual evoked responses were delayed. Examination of CSF showed oligoclonal bands. She was treated with high dose intravenous methylprednisolone, which was followed by gradual improvement. Three months later she experienced left sided facial weakness and coordination disturbances, and subsequently with intervals of about 3 months, she had three further relapses. Each relapse occurred during the premenstrual period (1 to 4 days before menstruation), and was treated with a course of high dose intravenous methylprednisolone. During the next 2 years her condition was stable; at the last visit her EDSS was 2.5.

Patient 3 was a 33 year old nulliparous woman in previous good health who experienced numbness in the right side of her body. She did not use an oral contraceptive. On examination there was diminution of touch, pinprick, and proprioceptive sensation over the right side of the body. The tendon reflexes on the right side were brisker, and a right Babinski's sign was present. Brain MRI showed multiple hyperintense white matter lesions in the periventricular areas, cerebellum, and pons on T2 weighted sequences. Examination of CSF showed oligoclonal bands. In December 1994 she was admitted to hospital because of weakness in the right arm and numbness in the left arm and leg. Symptoms had started 2 days before onset of menstruation. She was treated with high dose intravenous methylprednisolone, resulting in gradual improvement. Between December 1994 and March 1996 she had 5 further relapses, occurring with intervals of 3 months. All relapses started 1-4 days before menstruation, and were treated with a course of high dose intravenous methylprednisolone (figure). After exacerbation in March 1996 she was treated with subcutaneous INF- $\beta$ -1b and she started a vegetarian diet. There were no further relapses up to her last visit in July 1997.

These 3 women with relapsing-remitting multiple sclerosis had a particular disease course, characterised by exacerbations that occurred exclusively during the premenstrual period. This is probably different from the premenstrual transient worsening of existing symptoms which occurs in many women with relapsing-remitting multiple sclerosis.<sup>3</sup> However, we cannot exclude that the underlying mechanism is different and that the patients described here may be at one end of a range. Exacerbations in the premenstrual period are likely to be triggered by dynamic changes in sex hormone concentrations. Before the



Relation between changes in EDSS and the menstrual cycle in patient 3.

menstrual bleeding there is a sudden fall in circulating levels of progesterone and oestradiol. Both sex steroids have numerous regulatory effects on the immune system, including an influence on T cell populations, and the production of cytokines.<sup>4,5</sup>

Inflammatory cytokines, or so called Th1 cytokines, such as INF- $\gamma$ , tumour necrosis factor- $\alpha$  (TNF- $\alpha$ ), and interleukins 1 and 2 (IL-1 and IL-2), seem to play a key part in the generation of exacerbations in multiple sclerosis.<sup>6</sup> Pathways through which sex steroids influence the immune system are complex and incompletely understood. Oestrogens may inhibit the release of Th1 cytokines, such as IL-1 and TNF- $\alpha$ , whereas progesterone may enhance the release of Th2 cytokines, which inhibit the production and activity of the Th1 cytokines.<sup>7-9</sup> Thus the abrupt withdrawal of progesterone and oestradiol in the premenstrual phase may shift the balance in favour of the production of inflammatory Th1 cytokines. Also, other hormones, such as inhibin, may contribute to this effect. The circulating concentration of inhibin, a hormone which decreases INF- $\gamma$  production, also sharply declines just before the menstruation.<sup>10</sup> Changes in concentrations of circulating sex hormones during the menstrual cycle were also found to influence disease activity in other putative autoimmune disorders, including rheumatoid arthritis, systemic lupus erythematosus, and autoimmune thyroid disease.<sup>5, 11, 12</sup>

An important question that needs to be investigated is whether the premenstrual period is an independent risk factor for exacerbations in the whole female multiple sclerosis population. This should be examined by a large prospective study. Unravelling the roles of sex hormones in the immune system and cytokine network that may regulate disease activity in multiple sclerosis may provide clues for the development of new therapeutic strategies.

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## CORRESPONDENCE

### Autonomic effects of selegiline: possible cardiovascular toxicity in Parkinson's disease

(1)

We read with interest the article by Churchyard *et al*<sup>1</sup> showing that selegiline in combination with levodopa was associated with significant impairment of the normal reflex responses controlling blood pressure to head up tilt and standing. It was suggested by the authors that this could be one explanation of the finding of increased mortality in the combined levodopa/selegiline arm of the Parkinson's Disease Research Group of the United Kingdom trial.<sup>2</sup> We are currently conducting a study investigating the cardiovascular reflexes in patients recruited from a community disease register for Parkinson's disease, diagnosis being based on identical clinical diagnostic criteria to the reported study. Patients were excluded from the study if they were known to have diseases associated with impaired autonomic system function or if they were currently being treated with drugs other than those for Parkinson's disease. We have identified 27 such patients, five receiving selegiline and levodopa and 22 receiving levodopa. With similar techniques and equipment as the authors we have measured orthostatic blood pressure at 1 minute, Valsalva ratio, and heart rate on standing (30:15 ratio). Age, sex, duration of disease, Webster scale, and daily levodopa dose did not differ significantly between the group of patients on levodopa alone and on levodopa and sel-

egiline combined (table). There was no significant difference in the results of autonomic function testing between the two groups with analysis of variance (ANOVA) and *t* tests. Both groups of patients showed falls in blood pressure on standing and this did not seem to be more pronounced in the group on levodopa plus selegiline compared with patients on levodopa alone. This finding is surprising given the much lower dose of levodopa prescribed in our study compared with that of Churchyard *et al*. However, our failure to show significant hypotensive interaction between selegiline and levodopa may have resulted from the lower dose of levodopa prescribed in our study. We did not specifically look at blood pressure changes during 45° head up tilt. As yet we have not been able to retest patients in whom selegiline has been withdrawn to see if any significant changes become apparent. In view of the small sample sizes reported by Churchyard *et al* and our own study, we think that both sets of results should be interpreted with caution. In elderly patients with Parkinson's disease even modest doses of levodopa seem to be associated with orthostatic hypotension. It seems unlikely that the additional hypotensive effect of selegiline could be the sole explanation of the apparent increased mortality with levodopa and selegiline compared with levodopa alone.

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- 1 Churchyard A, Mathias CJ, Boonkongchuen P, et al. Autonomic effects of selegiline: possible cardiovascular toxicity in Parkinson's disease. *J Neurol Neurosurg Psychiatry* 1997;63:228-34.
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(2)

We have read with great interest the article by Churchyard *et al*<sup>1</sup> that appeared in the *Journal*. There are several issues that we comment on.

The study design is not scientifically sound: the trial is not randomised, the number of patients in the two groups is unequal, and half of the patients were selected from an earlier study.<sup>2</sup> According to the authors the two groups were matched for age, duration, and severity of the disease, and the dose of levodopa. Due to the study design the patients could not, however, be matched according to the autonomic functions, although there were no significant differences in the occurrence of clinical postural dizziness. The change in the systolic blood pressure after standing was, however, significantly lower in the selegiline group (group II) after the withdrawal than in the group receiving only levodopa (group I). Also one patient in group I had a clear hypertensive reaction (systolic blood pressure >200 mm Hg) while standing. This suggests that the autonomic function in group II even without selegiline was more compromised than in the group I, thus showing a selection bias.

It is not, however, a new finding that orthostatic hypotension could occur when

Table 1 Mean (SEM) median indices for patients taking levodopa only or levodopa and selegiline

	Levodopa (n=22)	Selegiline (n=5)
Age (y)	71.7 (1.7) 72	64.8 (6.6) 66
Duration (y)	6.6 (0.9) 5.5	7.0 (1.9) 5.0
Webster scale	13.4 (1.4) 15	11.4 (2.1) 10
Daily selegiline dose (mg) (mean duration 7 y)		10
Daily levodopa dose (mg)	433 (43) 350	560 (254) 400
Supine systolic BP	158.8 (5.3) 158	143.6 (7.6) 145
Standing systolic BP	147.7 (5.9) 143	133.6 (10.8) 143
% Change systolic BP	-7.6 (-1.6) -8.4	-7.5 (-3.1) -6.5
30:15 Ratio	1.03 (0.01) 1.02	1.04 (0.02) 1.06
Valsalva ratio	1.16 (0.03) 1.15	1.2 (0.01) 1.19

selegiline and levodopa are given together. Orthostatic hypotension is often found in late stage Parkinson's disease due to autonomic disturbances.<sup>3</sup> All dopaminergic drugs such as levodopa or dopamine agonists have been shown to cause orthostatic hypotension.<sup>4</sup> In a recent double blind study Turkka *et al*<sup>5</sup> prospectively followed up patients in a double blind study measuring autonomic function with a similar method to Churchyard *et al*<sup>1</sup> for several years. They found that with time there was significantly more orthostatic hypotension assessed with the tilt test in the selegiline plus levodopa group than placebo plus levodopa group. However, only two out of 27 patients in the selegiline group fulfilled the criteria of orthostatic hypotension.

The mode of action of orthostatic hypotension with dopaminergic drugs is not clear. Selegiline is known to potentiate the therapeutic effects of levodopa but also its adverse effects if the dose of levodopa is not reduced sufficiently.<sup>6</sup> The authors claim that selegiline would impair the noradrenaline and heart rate responses to tilt although no significant changes were detected between the groups. The authors make hasty conclusions that selegiline would be cardiotoxic with no scientific verification. If a drug causes orthostatic hypotension it does not mean that the drug would be cardiotoxic!

Furthermore, the authors showed that the clinical condition of the patients deteriorated considerably after withdrawal of selegiline. As the disability was considerably worse after the withdrawal than during selegiline treatment, the effect of adequate dopaminergic medication on cardiovascular responses remains unknown. It is possible that adding a sufficient amount of dopaminergic medication to group II after withdrawal of selegiline would cause similar orthostatic hypotension to that found when selegiline was combined with levodopa. Indeed, Kaufman *et al*<sup>7</sup> analysed patients with Parkinson's disease with orthostatic hypotension and found no significant difference between patients treated with levodopa, dopamine agonist, or the combination of selegiline and levodopa.

Finally, the authors suggest that their findings would be related to the metabolites of selegiline. The authors did not take into account that these amphetamine metabolites are of levoform. Furthermore, d-methamphetamine or d-amphetamine often cause increases of blood pressure, not hypotension.<sup>8</sup> Similarly, there is a dose proportional increase of blood pressure in rats caused by d-p-hydroxy amphetamine or d-p-hydroxy-norephedrine.<sup>9</sup> The authors imply that selegiline would cause withdrawal effects in humans and refer to an experimental study on rats (<sup>33</sup> cited by Churchyard *et al*<sup>1</sup>). The authors also suggest that selegiline loses its selectivity during treatment. A postmortem study showed, however, that there was no increase of monoamine oxidase-A inhibition along with long term selegiline treatment.<sup>10</sup>

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#### The authors' reply:

Heinonen and Myllylä have raised several issues relating to our recent article which appeared in *J Neurol Neurosurg Psychiatry*.<sup>1</sup> As they note, the study, which examined autonomic function in those on long term treatment (mean >5 years), was of necessity not randomised. However, selection bias was minimised by recruitment of all outpatients on levodopa and selegiline or levodopa without selegiline within a given time and regardless of the presence or absence of symptoms suggestive of autonomic dysfunction. That there was no bias towards more severely affected cases being placed on selegiline is strongly suggested by the excellent match between the two groups for age, duration and severity of disease, and the dose of levodopa and the greater frequency of symptomatic postural dizziness in those on levodopa alone. Moreover, as noted by Heinonen and Myllylä, the combination of selegiline and levodopa was also associated with a higher incidence of postural hypotension than levodopa and placebo in a prospective, randomised double blind study.<sup>2</sup> Heinonen and Myllylä note that the percentage change in systolic blood pressure, but not the absolute levels, was lower in those previously on selegiline and levodopa three months after withdrawal of selegiline than in those originally on levodopa alone. However, both the standing systolic blood pressure and the percentage drop were greater than when patients were taking selegiline and levodopa. That is, the hypotensive effects of standing had improved three months after stopping selegiline even though the average daily dose of levodopa had been increased (not significant) and seven (44%) patients required addition of the potentially hypotensive ergolene pergolide. This suggests that the orthostatic effect was specific for selegiline and levodopa rather than a non-specific consequence of dopaminergic treatment itself. Therefore, we think that our finding that selegiline and levodopa cause orthostatic hypotension is robust and represents an unwanted and potentially dangerous drug interaction.

Coyle, *et al* examined standing systolic blood pressure, Valsalva ratio, and 30:15 ratio in 22 patients on levodopa alone and five on

selegiline and levodopa. They found that standing precipitated a small and asymptomatic fall in systolic blood pressure that was similar in both groups and by contrast with our finding that levodopa and selegiline caused a greater drop in standing systolic blood pressure than levodopa alone.<sup>1</sup> However, the number of those on selegiline and levodopa was small and, as Coyle *et al* note, the daily dose of levodopa was lower. Moreover, although both groups were apparently matched, the mean age of those on levodopa alone was seven years more than those on the two drugs and the SEM of age of those taking selegiline and levodopa was 10%, implying a much greater age range in this group and so raising the possibility that increased orthostatic hypotension in those on levodopa alone as a result of aging<sup>3</sup> might have exerted a confounding influence on their data.

Coyle *et al* reasonably caution that autonomic function has been examined in only a few published cases. Collectively, we<sup>1</sup> and Turkka *et al*<sup>5</sup> have studied 43 patients on levodopa and selegiline with both groups finding that the combination of drugs was associated with greater orthostatic hypotension than levodopa alone. In a separate study of 20 patients on selegiline (unpublished data) we have again found a similar impairment of cardiovascular reflexes which occurred as a result of selegiline and levodopa treatment. Thus, we think that our findings indicate that the combination of selegiline and levodopa impairs cardiovascular control in at least some and perhaps even a majority of patients with moderately advanced or severe Parkinson's disease.

We agree with Heinonen and Myllylä that the causes of orthostatic hypotension induced by selegiline and levodopa are unknown. We considered two potential causes: an amphetamine effect or increasing inhibition of monoamine oxidase-type A which might be expected to increase plasma concentrations of the false transmitter tyramine, which also causes orthostatic hypotension.<sup>4</sup> Selegiline may lose some of its selectivity for monoamine oxidase type B at high doses or with chronic treatment at <10 mg/day.<sup>5-7</sup> Riederer *et al* found that >65% of monoamine oxidase type A activity was inhibited by treatment with selegiline at 5-10 mg/day in the brains of seven patients with Parkinson's disease and noted that the degree of inhibition of monoamine oxidase type A seemed to rise with increasing duration of treatment.<sup>8</sup> Selegiline comprises the l-isomer of deprenyl and is thought to be largely metabolised to l-amphetamine and l-metamphetamine<sup>9</sup> which have less potent cardiovascular toxicity than the d-isomers. Although amphetamines cause supine hypertension, they have also caused orthostatic hypotension by impairing sympathetic function in humans.<sup>10</sup> To our knowledge cerebral and plasma concentrations of the l-isomers and d-isomers of amphetamine have not been measured in those on long term selegiline treatment. Thus the possibility that high cerebral or plasma concentrations of l-amphetamine and l-metamphetamine sufficient to cause toxic cardiovascular effects as a result of long term treatment with selegiline and levodopa cannot be excluded. In the submitted study of 20 patients on selegiline already referred to we found that the impaired cardiovascular reflexes due to selegiline and levodopa treatment normalised within four to seven days of stopping selegiline. This time course was consistent with either an amphetamine effect

or loss of selectivity for monoamine oxidase type B resulting in excess plasma tyramine. However, in this study selegiline seemed to cause supine hypertension as well as orthostatic hypotension. This combination would be consistent with either an amphetamine or a tyramine effect.

The failure of patients with severe orthostatic hypotension induced by selegiline and levodopa to develop a compensatory tachycardia indicates impairment of cardiovascular reflexes<sup>1</sup> and as such is consistent with significant, albeit reversible, drug toxicity by whatever mechanism.

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#### Idiopathic generalised epilepsy in adults manifested by phantom absences, generalised tonic-clonic seizures, and frequent absence status

I read with interest the report by Panayiotopoulos *et al.*<sup>1</sup> Their series recalled a 58 year old man who presented for evaluation after several episodes presumed to be complex partial status epilepticus. His neurological history was remarkable only for two convulsions in his late teens which led to his discharge from the armed forces. He did not recall whether these seizures were related to sleep deprivation or alcohol withdrawal. He did not recall being informed of seizures, staring spells, or other paroxysmal events as a child. He denied a family history of seizures or other neurological diseases. He was treated briefly with phenytoin, but was free of seizures and took no anticonvulsant drugs for almost 40 years, when he began to experience episodic confusion lasting for hours. Interictal EEGs were reported to show spike wave discharges. Brain MRI was normal. He was treated with various combinations of phenytoin, carbamazepine, phenobarbitone, and primidone, which did not prevent these confusional episodes. Video EEG monitoring

after withdrawal of all antiseizure medications showed frequent bursts of 3-3.5 Hz spike wave activity. Hyperventilation produced clinical and electrographic seizures lasting  $\geq 8$  minutes at a time, and terminating spontaneously. The patient became confused, was unable to follow simple commands, answer questions, or repeat simple phrases. Electrographically, these seizures consisted of bisynchronous, frontally predominant spike wave discharges which began at 3.5 Hz but slowed to 2.5 Hz over several minutes. At the end of each seizure, the patient was immediately alert and able to follow commands, converse, and repeat. Treatment with divalproex (750 mg/day) abolished the seizures and the interictal EEG abnormalities for four years. The patient did not wish to attempt withdrawal from divalproex, and was returned to the care of his family physician.

I would like to ask the authors whether their patients manifested an EEG or clinical response to hyperventilation.

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- C P Panayiotopoulos, M Koutroumanidis, S Giannakodimos, et al. Idiopathic generalised epilepsy in adults manifested by phantom absences, generalised tonic-clonic seizures, and frequent absence status. *J Neurol Neurosurg Psychiatry* 1997;63:622-7.

#### Panayiotopoulos *et al* reply:

We thank Bleck for vividly illustrating the challenging diagnostic and management problems of these patients that were among the main purposes of our report. His patient, like ours, had infrequent generalised tonic clonic seizures with onset in the late teens and frequent episodes of absence status that was misdiagnosed as complex partial status epilepticus. Also, he probably had phantom absences during interictal generalised 3-3.5 Hz spike and slow wave discharges but this needs documentation with breath counting or other means of testing for mild impairment of cognition. Similarly to our cases, he was also erroneously treated with phenytoin, carbamazepine, and barbiturates for many years and seizures stopped only when appropriate medication of divalproex was prescribed. He was fortunate not to receive vigabatrin, which exacerbates absences and absence status.

The only difference from our cases is that Bleck's patient had prolonged, 8 minute, severe absence seizures provoked by hyperventilation after withdrawal of all antiseizure medication. Although briefer, this was similar to the absence status in our patients; this severe electroclinical state was documented only during spontaneous absence status, not during hyperventilation. However, in all patients over-breathing increased the generalised 3-4 Hz spike or polyspike and slow wave discharges that were often associated with mild impairment of cognition, shown with errors of breath counting. Hyperventilation was the only means of inducing generalised 3-4 Hz spike and slow wave discharges in some of the patients whose resting EEG could be normal. This is in accordance with the provoking effect of hyperventilation on absences of the idiopathic generalised epilepsies.

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## BOOK REVIEWS

### The Neuropathology of Dementia.

Edited by MARGARET M ESIRI and JAMES H MORRIS. (Pp 440; £75.00.) Published by Cambridge University Press, Cambridge. 1997. ISBN 0-521-43311-8.

This distinguished pair of Oxford neuropathologists offer a new book to the "pathologist faced with the task of determining the cause of dementia in cases requiring post-mortem diagnosis". They are credited with editorship; actually, they have written 11 chapters and two appendices, among them those chapters which deal with the pathological processes which account for 90% of adult dementia (Alzheimer's disease, vascular disease, and Lewy body disease). For the remaining eight chapters and appendix, Professor Esiri and Dr Morris recruited acknowledged experts.

After an introductory chapter on dementia, which describes the clinical syndrome and describes its neuroanatomical basis, there are two chapters in which Esiri and Morris define the practical approach to the pathological diagnosis of dementia. The first of these chapters describes (and illustrates diagrammatically) the neuroanatomical structures which are particularly pertinent to cases of dementia. The diagrams of neural connectivity in the hippocampus and neocortex may daunt the general pathologist, but the chapter provides a useful summary of pathological processes which affect each anatomical region of the brain; that is to say, it offers a regional approach to the differential diagnosis of dementia. The second of these chapters gives instruction on the conduct of the post-mortem in a case of dementia, details the observations which should be made on the unfixed brain at the time of postmortem, and on the fixed brain, and provides a scheme for the selection of tissue blocks and histological stains.

The rest of the book is composed of chapters which are dedicated to individual causes of dementia, starting with the commonest diseases: Alzheimer's disease, vascular disease, and Lewy body disease. The very numerous rare causes of dementia are all discussed in subsequent chapters, which include adequately comprehensive and up-to-date accounts of aetiology and pathogenic mechanisms, but manage to retain the practical perspective; a mark of successful editorship. I should emphasise that this book is not simply a practical manual although it largely succeeds in that respect. It succeeds also in taking a common sense approach to issues which are controversial among neuropathologists. The general pathologist who turns to this book will receive sound advice on such matters as the pathological diagnostic criteria of Alzheimer's disease and its distinction from age related changes, on the relation of head injury to the pathogenesis of Alzheimer's disease, and on the range of clinical and pathological phenotypes which are included

variably under the eponymous label of Pick's disease.

Yet in some instances, the editors do not take the generalist's side. Surely, it is unreasonable to recommend special neuro-histological techniques like Cajal's gold chloride, the silver impregnations of Bielschowsky and Cross, and Holzer's method, when the information which these preparations provide can be obtained with the immunoperoxidase techniques which are in everyday use in the general histopathology laboratory. Antibodies against  $\beta$ A4-peptide, paired helical filament-related tau epitopes, ubiquitin, glial fibrillary acidic protein, and neurofilament protein are commercially available, and the technique is standard, of reproducible quality, and may be automated. Diffuse and neuritic forms of the senile plaque, neurofibrillary (tangle) degeneration, Pick bodies and Pick cells, cortical Lewy bodies, the cortical neuronal inclusions of motor neuron disease, and astrocytic gliosis are all easily demonstrated with this panel of antibodies. There is merit in recommending the combined Luxol fast blue and cresyl violet preparation (which stains myelin sheaths blue and neuronal perikarya purple, when properly done) because it offers considerable help with anatomical localisation of individual nuclei and fibre tracts in sections of basal ganglia and brain stem. However, plaques of demyelination are just as easily diagnosed on haematoxylin and eosin stained sections, so that the pathologist who is confident of anatomical landmarks can dispense with traditional myelin stains too.

I am disappointed with the index. Look up ubiquitin and none of the page numbers to which you are referred will tell you about its value in identifying cortical Lewy bodies. Look up tau and you will be referred to pages about neurofibrillary tangles but not to the sections on Pick bodies or the tangle-like inclusions of corticobasal degeneration. There are other examples.

The reader is also let down with some of the illustrations. It is gratifying to find a substantial neuropathology textbook selling for significantly less than £100 but a book which is intended to assist someone peering down a microscope at coloured histological preparations should have many more colour photographs. Surely, modern publishing technology can produce colour illustrations and still keep to moderate prices. Also there are several errors. Two examples will make the point: the two photographs in figure 3.12 (a) and (b) are wrongly positioned in relation to the legend, and the photographs in figure 5.10 are clearly from luxol fast blue preparations (indeed it says so in the legend) but the stain/magnification label says H&E.

One other niggle is the tendency, in a few chapters, for the authors to overreference the texts. As the style of referencing is that of authors and year of publication, rather than

numerical superscript, overreferencing can make a chapter unpleasant to read and impossible to scan for particular information (such as a key word from the index). David Mann's chapter on Down's syndrome is a particular example of the way in which references pepper the text like an obstacle course.

The remarks in the last four paragraphs do not diminish significantly my admiration for this book. I concur with the view of Sir Bernard Tomlinson who remarks, in the *Forward*, that "the principal authors have, through their own clear accounts, their perceptive insight into pathologists' needs, ...produced a book which will be a most welcome addition, and perhaps a treasure, in many laboratories, clinical libraries and personal collections". I am very pleased to have it and I recommend its purchase.

JOHN XUEREB

**Oxford Core Texts, Neurology.** By MICHAEL DONAGHY. (Pp 221; £14.99). Oxford: Oxford University Press, 1997. ISBN 0-19-262795-3.

"A detailed neurological examination is . . . a test of concentration and cooperation (even) in those in good health. . . . It may be necessary to conduct the examination in more than one session". These are not quotations from Michael Donaghy's attractive book but from a book on clinical methods published in 1968. Comparison of this with Donaghy's book provides a clear demonstration of how clinical neurology, not just neuroscience, has advanced in the intervening 30 years. Generations of medical graduates have been discouraged about neurology because of the overwhelming (and often overbearing) way in which it was taught. Donaghy's book is representative of a more realistic way of teaching neurological clinical methods which hopefully will produce a new generation of clinicians practising neurology as a practical science. In particular the neurological examination is portrayed as a set of techniques to be applied as appropriate to the clinical problem at hand, rather than an arcane (and mentally taxing) ritual played out with the mind in neutral.

After an initial chapter discussing important parts of the neurological history a basic neurological examination is well described and illustrated. Here the only obvious omission is the valuable test of asking patients to outstretch their arms with supinated hands and closed eyes, a very sensitive screen for significant neurological deficit in the upper limbs, widely used by neurologists in practice. Subsequent chapters pursue more detailed examination techniques in the context of specific clinical problems. This approach works well and is complemented by the later

chapters reviewing common neurological syndromes. Management is touched on, including telling patients about incurable disease, but assessment of disability, as opposed to deficit, is not much considered.

The aim of the book is to provide students with "a working knowledge of common clinical problems in neurology, and teach a simple, quick, and reliable neurological examination". This is what medical students require to cope with the neurology they will meet as junior hospital doctors and on which they can build if they decide to become physicians, general practitioners, or even neurologists. In my view the author succeeds in his aims and is to be congratulated on producing a well illustrated and laid out paperback introduction to neurological clinical methods. Students in my university will be particularly amused to see the photographs of Donaghy testing the muscular strength of a member of the Oxford University Boat Club!

CHRIS ALLEN

**Myasthenia Gravis.** By HJGH OOSTERHUIS. (Pp 252 DG60). Groningen: Groningen Neurological Press, 1997. ISBN 90-9010600-6.

Oosterhuis is a well known figure in the world of myasthenia gravis, has published extensively on the subject, and clearly has accumulated the depth of experience on the subject that only comes with time. However, this book is not simply a review of the subject but a very personal account of the years he has spent managing 800 patients with the disease in his native Holland. It is a delightful read from the historical aspects, which are so important to understand the therapeutic options and relative benefits in contemporary medicine to the explanation of differential diagnosis. Also he covers in succinct detail the epidemiology of myasthenia and reviews the diagnostic criteria and tests, as well as the treatments now available for this condition which is the archetypal immunologically mediated neurological disease. The book is extremely well illustrated with historical and clinical photographs and diagrammatic representations of disease course with relation to different serological and clinical indices. If there was any criticism to be levelled at this book it would be that the frequency of spelling mistakes and typos can be a little irritating, but then I am sure my Dutch would be worse. I would recommend anyone who has a specific interest in myasthenia or indeed those who are likely to come across the disease in clinical practice to acquire this book, they will not regret it and it will continue to be a relevant clinical guide for many years.

NEIL ROBERTSON