diagnosis of polyneuritis cranialis.

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Respiration and sleep in Parkinson's disease

Sir: We have read with great interest the recent paper by Apps *et al.*¹ on respiration and sleep in Parkinson's disease. We were particularly intrigued by the finding of an increase in respiratory rate among the Parkinson subjects compared with control subjects while awake and during REM sleep. It would be important to know if any direct measurement of minute ventilation or end tidal CO₂ was performed, that is, whether the tachypnoea was associated with true hyperventilation. Also, we wonder if their subjects had pulmonary function testing, as restrictive lung disease is often accompanied by increased respiratory frequency.

The authors appropriately point out that one possibility for this finding is an alteration of ventilatory control in Parkinson's disease. As there is a great deal of evidence that central catecholamines play a role in ventilatory drive,² this is a very reasonable speculation.

We have recently studied ventilatory drive in a group of 14 patients with Parkinson's disease (Hoehn and Yahr stages III-IV) and 11 age matched controls. All subjects had spirometry to rule out significant obstructive or restrictive lung disease. We did not observe changes in resting end tidal CO₂ or respiratory rate at rest in our group of Parkinson's patients. However, using rebreathing methods for hyperoxic hypercapnia and isocapnic hypoxia^{3,4} we found an increased response in our Parkinson's disease subjects to both hypercapnia and hypoxia.⁵ It is not yet clear whether this might be a central effect or whether dopamine metabolism in the carotid bodies of these patients is abnormal as well.

Further studies of ventilatory drive in

Parkinson's disease should be of considerable interest both to expand our knowledge of this disease and to elucidate further the role of catecholamines in respiratory drive in man.

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Apps replies:

I myself have carried out studies of hyperoxic hypercapnic rebreathing in Parkinsonian patients and found a normal response to this diminished breathing though some of the patients had an end tidal CO₂ at the lower end of the normal range.

Sensorimotor neuropathy and cisplatin and adriamycin toxicity

Sir: The brief report by Pages *et al.*¹ of a severe sensorimotor neuropathy developing in a subject treated with adriamycin and cisplatin raises a number of interesting mechanistic questions. As they note, the occurrence though transient of a motor component to the neuropathy was unexpected and is as yet inexplicable. Neither of these drugs penetrates the normal blood-brain barrier² and this is shown by the low concentrations of cisplatin found in the CNS, although cisplatin may have access to peripheral nerve.³ Both drugs must readily

enter the spinal ganglia, presumably through fenestrations in the vascular bed noted some years ago.⁴ Another possible route to motor nerves through their terminals is available,⁵ but this is likely to be very minor by comparison, although with the very high dose of cisplatin given (about twice the amount usually considered to be neurotoxic) this route could conceivably have become more important.

The well known damage to sensory nerve fibres encountered in cisplatin intoxication is a different, and perhaps more straightforward, matter. The reduction in numbers of myelinated and unmyelinated axons in the sural nerve biopsy of this reported case confirms this and would be anticipated to be due to severe damage to their cell bodies within sensory ganglia, if our recent experimental studies in rats have any relevance to the matter.⁶ While in this species it in fact has not been possible to reproduce the neuropathy, (for the animals die of non-neurological causes when the cumulative dose reaches only about 150 mg/m², which is about half the dose required to cause neuropathy in man), there is nevertheless unequivocal damage to nucleoli in a high proportion of sensory ganglion cells. This becomes visible within the first 24 hours of treatment with cisplatin and proceeds to segregation of the nucleolar constituents and later nucleolar fragmentation. Since nucleoli are the seat of ribosomal synthesis and nucleolar segregation is a sign of reduction or cessation of synthetic activity, it was not perhaps surprising to find that by the end of a week of treatment many ganglion cells showed severe reduction in Nissl material and conspicuous shrinkage of the whole cell. If the animals had not died from other causes, it is highly likely that cell death and/or axonal degeneration would have shortly followed, for these cellular events, while not precisely the same as those found with adriamycin in rat spinal ganglia, followed the same general sequence. Indeed, both drugs have somewhat analogous effects upon DNA and lead particularly to inhibition of RNA polymerase I activity,^{7,8} the polymerase concerned with ribosomal transcription. In cisplatin toxicity ganglion cells are randomly affected regardless of size, and since small neurons responsible for unmyelinated and thinly myelinated fibres are substantially more numerous than large neurons concerned with the more discriminatory aspects of sensation, it is not wholly surprising that cases of neuropathy should occasionally show very little in the way of sensory loss of the latter type. The sural nerve biopsy showed in this case a substan-