diagnosis of polynueuritis cranialis.

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References


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 isoapnic hypoxia3,4 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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References


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 al7 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 barrier4 and this is shown by the low concentrations of cisplatin found in the CNS, although cisplatin may have access to peripheral nerve.5 Both drugs must readily enter the spinal ganglia, presumably through fenestrations in the vascular bed noted some years ago.6 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 seggregation of the nucleolar constituents and later nucleolar fragmentation. Since nucleoli are the seat of ribosomal synthesis and nucleolar seggregation 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 The polymerase concerned with ribosomal transcription. In cisplatin toxicity ganglion cells are randomly affected regardless of size, and since small neurons responsible for unmetylated 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-
Matters arising

tial fibre loss in the smaller range that would be expected to come from small sensory neurons.

How much of the neuronal damage was caused by cisplatin and how much by Adriamycin cannot be stated, of course, but Adriamycin has always been said by clinicians not to produce a sensory neuropathy; but the ability to detect clinical damage to small sensory neurons is rather limited. From what we know of the mode of action of this and similar agents it is possible that this insensitivity to Adriamycin toxicity is more apparent than real. Only careful future studies will show where the truth lies.

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Visual field rehabilitation in the cortically blind?

Sir: Recently, Balliet et al reported that, in contrast to our work, they were not able to find any effect of specific treatment on visual field recovery in 12 patients suffering from homonymous visual field loss due to unilateral ischaemic or embolic posterior artery infarctions. As it stands, the paper deserves some comment because Balliet et al obviously misinterpreted our data and our discussion, drawing misleading inferences about our results from their data. We called Balliet et al's attention to this discrepancy in detail in a personal letter in July 1983 which Balliet et al ignored completely. We would like, therefore, to clarify some major points.

It seems as if Balliet et al concluded from our work that every patient suffering from homonymous field loss could be treated successfully, otherwise one cannot understand why they concluded from their data that "visual field increases are not trainable". This generalised conclusion has never been drawn by us. When we started this investigation in 1976 our main interest was to find out whether field defects can in principle be reduced by treatment. The question as to how frequent and to what extent training effects can be expected in a large group of patients is another aspect; while perhaps important from the clinical and rehabilitative viewpoint, it must not be confused with the first, more fundamental one. This latter aspect has been addressed by us in two recent papers. We can, therefore, not see how Balliet et al, on the basis of their data, can conclude, that visual field defects cannot be treated at all. They would have been correct in stating that in their 12 patients they were not able to find any effect. In the light of our own data this is by no means a surprise, because (as pointed out above) one cannot expect field enlargement in every patient showing homonymous field loss.

It has long been known that irreversible damage to the striate cortex and its afferents (optic tract, optic radiation) causes permanent blindness. On the other hand, observations on spontaneous recovery and recovery after systematic treatment in patients with cerebral damage suggest that in some cases the functional loss may, at least in part, be due to reversible damage. Unfortunately the nature of structural damage in terms of irreversible/reversible, at least at the moment, cannot be determined reliably. Therefore, it is impossible to predict which patient may benefit from treatment and which not. In a recent article we reported that return of visual field portions were observed only in cases with incomplete damage, as evidenced by, for example, lowered CT density values, whereas in cases with complete damage (pseudocystic necrosis) we could not find any evidence for visual field enlargement.

2 Having failed to find any effect of their method of visual field training Balliet et al conclude that our results may be due to artifacts resulting from "any combination" of (a) large stimuli variability in perimetric testing, (b) changes in detection strategies with practice and (c) eccentric fixation. These assertions can easily be tested for since (a) large stimulus variability as well as changes in detection strategies should lead to inconsistent shifts of the border of the visual field (including artificial enlargement as well as shrinkage) and (b) eccentric fixation would result in an overall shift of the field border towards the affected side.

Regarding measurement variability, the range of perimetric measurement variability in our studies was +/- 0.5° within 15° eccentricity, and +/-1.75° beyond which is in good agreement with other authors (see ref 3). Considering this range of measurement variability one is surprised to learn that Balliet et al, in their study, found variations up to 40° (mean: 15°) but it is even more astonishing that these authors, on the basis of their measurement variability, conclude that our data can be explained on the basis of their inaccuracy in perimetric testing. Patients with such large variations would never have been included in our series. However, even if we accept the variability Balliet et al found for their normals in the far periphery of the visual field (between 1° and about 5°) we are not in a position to explain the field enlargement in our studies simply as measurement variability because field enlargement was in many of our cases much larger. Eccentric fixation, which may be additive, as Balliet et al suggest, but did not test, thus leading to an artificial field increase in the perimeter, can also not explain our results nor can changes in head position. In both cases one would expect that visual field should increase along the whole field border or at least along each meridian where training has been performed. Our data show clearly that this is not the case. In contrast, recovery was incomplete in all cases and field enlargement was limited to particular field regions and was not observed in any field portion subjected to training which should be the case if Balliet et al were right. Furthermore, as Teuber et al have shown, the blind spot should also change its position in correspondence with eccentric fixation. However, we did not find any evidence for such a change. Finally one should, in addition, also keep in mind that any combination of these factors could also lead to changes in the reverse direction, that is, to a reduction of the extent of visual field (see, for example reference 4).
Sensorimotor neuropathy and cisplatin and adriamycin toxicity.

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