SIR: Förstl *et al* (*Journal*, March 1993, **162**, 385–392) presented a prospective longitudinal study designed to investigate frequency, clinical manifestations, and neuropathological findings of the Lewy body (LB) variant of Alzheimer's disease (AD). At post-mortem analysis, LBs were found in the cortex and brainstem of eight out of 65 patients with the clinical diagnosis of possible or probable AD. In patients with LB pathology (LBP), computerised tomography scans showed cortical atrophy which was most pronounced at the frontal lobes. The neuropathological analysis revealed that the presence of LBs was accompanied by a dramatic cell loss in the *intermediate* component of the nucleus basalis of Meynert (nbM). Neuron counts in the nbM were significantly lower in patients with LBs than in those without. Therefore the authors emphasised the prominence of cholinergic dysfunction in the LB variant of AD. We wish to draw attention to some issues of this interesting paper.

(a) In our opinion, the degenerative changes affecting the basal forebrain of patients with LBP appear to correlate with the cortical atrophy which was found in the study by Förstl *et al*. Previous investigations performed on AD brains suggested that the involvement of the nbM is most likely a consequence of primary cortical pathology (Pearson *et al*, 1983) which results in a decrease of trophic factors retrogradely transported to the basal forebrain (Hefti & Weiner, 1986). The localisation of low-affinity nerve growth factor (NGF) receptors on the large cholinergic neurons within the nbM have indirectly indicated that these cells are strictly dependent on the NGF (Mufson *et al*, 1989*a*). This view is supported by experimental evidence showing that the depletion of choline acetyltransferase (ChAT) activity and the cell atrophy observed in the intermediate nbM of primate bearing a fronto-parietal cortical lesion can be prevented by exogenous NFG (Liberini *et al*, 1993).

It has been indicated that the severity and the localisation of the neuropathological changes affecting the cholinergic neurons within the basal forebrain follow a regional distribution which correlates with the regressive phenomena of the neocortex receiving the corresponding projections (Mufson *et al*, 1989*b*).

It is remarkable that in primates the intermediate nbM provides the major cholinergic input for the frontal cortex. Therefore, the greater neuronal damage in the nbM of patients with LBs than in those without is likely to depend on the frontal accentuation of the cortical atrophy detected in the formers by Förstl *et al*.

(b) Förstl *et al* detected significant cell loss in the nbM of all examined patients. This finding was obtained by counting neurons defined as large Nissl-positive nucleolated cells. On this regard, we would like to underline that, using an *a priori* criterion of neuron size as a working definition for basal forebrain neurons, various degrees of cell loss within the nbM were reported to occur in primary degenerative dementia. However, the cell atrophy occurring in the basal forebrain makes this size factor a less accurate criterion for the estimation of cell loss because shrunken but viable neurons may be counted as lost (Vogels *et al*, 1990). In contrast, by applying quantitative analysis to ChAT- or NGF receptor-immunostained preparations, both large and atrophied cholinergic neurons of the basal forebrain are counted, therefore reflecting more accurately the nbM's status (Liberini *et al*, 1993). This is of therapeutic relevance because atrophic but viable neurons may be still responsive to neurotrophins. In AD patients the permanence of immunoreactivity for high and low affinity NGF receptors on the nbM cholinergic neurons despite the severe atrophy supports this hypothesis (Mufson *et al*, 1989*b*).

(c) The prominent vulnerability of the cholinergic system in the LB variant of AD suggests that pharmacologic treatments directly or indirectly enhancing cholinergic transmission might ameliorate some of the impaired cognitive functions. Metabolic precursors of acetylcholine and inhibitors of acetylcholinesterase are, at present, the most promising molecules. Recently it has been shown that a subgroup of patients affected by primary degenerative dementia positively respond to direct manipulation of the cholinergic function obtained by administering the acetylcholinesterase inhibitor tacrine (Davis *et al*, 1992; Farlow *et al*, 1992). The question which naturally arises is whether in this group of responders a significant number of patients affected by LBP was included. We believe that the answer to this relevant question might come only from a post-mortem examination of the group of responders. A positive correlation would open new perspectives in the symptomatic treatment of a subgroup of demented patients.

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AUTHOR'S REPLY: What Edwards and co-authors do not seem to realise is that they have taken our point correctly. We are not at all convinced that the mere presence of cortical Lewy bodies in demented patients is sufficient evidence to propose a discrete β-amyloid dementia rather than a variant. We are delighted to hear that the authors have undertaken quantitative immunohistochemical studies using monoclonal antibody to β-amyloid protein. We have done that too and came to similar conclusions which we though were not worth reporting, because of the small number of cases in our study.

Liberini *et al* suggest an intriguing mechanism which may underlie the reported association between Lewy body pathology, cell loss or cell shrinkage in the basal nucleus of Meynert, and frontal lobe atrophy. This possible mechanism may offer an interesting therapeutic perspective.

McKeith *et al* (*Journal*, August 1993, **163**, 262–263) argue that the patients in our prospectively examined sample were biased so that they could not possibly satisfy their operational criteria. This is hard to believe as, for example, extrapyramidal disturbance, hallucinations (usually visual) or fluctuation due to temporary confusional state can occur in a large proportion of patients satisfying the NINCDS-ADRDA (McKhann *et al*, 1984) criteria (Förstl *et al*, 1992, 1993). The McKhann and McKeith criteria are not mutually exclusive. Therefore it would have been possible and of advantage if our patients with Lewy bodies had shown an increased rate of hallucinations, fluctuations, and so on. They did not. All eight were demented as required by the NINCDS-ADRDA criteria, five showed rigidity with cogwheeling and two had other 'psychiatric' disturbances. This is in good agreement with Lewy's original findings, who felt that

> "the psyche is seldom spared in the course of illness (of Parkinson's disease; transl. note). The mental symptoms may have different characteristics . . . but all belong to the group of senile dementia. In the early cases anomalies of affect prevail, partly of a euphoric, partly of a depressive nature; they are often associated with hallucinations and paranoid ideas derived from them. In the later years, the disturbance of memorizing and of memory predominate and lead to the most severe stages of dementia in a small number of patients" (Lewy, 1923; see Förstl & Levy, 1991).

We would be considerably concerned if traditional classification systems be abandoned (Almeida *et al*, 1992) in order to accommodate patients with dementia, paraphrenia or delusional depression and those with Lewy bodies in one group (together with 'preclinical' cases of odd cortical Lewy bodies), patients with dementia, paraphrenia and delusional depression without Lewy bodies in a second group, and 'other diseases' in a third.

Hughes *et al* (1992) have recently reported the neuropathological findings of 100 patients with clinically diagnosed Parkinson's disease. Similar to our series, all of their patients who had Lewy bodies in the brainstem also had Lewy bodies in the cortex. We would be interested to hear about these patients' cognitive status. It would certainly strengthen the Lewy body's role in psychiatry if some of those patients were demented, depressed or at least paraphrenic.

Should a significantly larger number of patients with cortical Lewy bodies be cognitively impaired, hallucinating, fluctuating, and so on, than Parkinson patients without cortical Lewy bodies, we will succumb to the ideas from Newcastle.

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