electromyography (SFEMG) showed improvement in all but one patient. Concentrations of AChR antibody decreased in four, increased mildly in two, and increased twofold in one patient who showed improvement according to clinical and SFEMG changes. However, changes in concentrations of AChR antibody were not correlated with clinical grading or SFEMG findings. Cytotoxic activity of NK cells, CD4/8 ratio, and the $CD4^+$ T lymphocyte count increased during the treatment but not significantly. No side effects were detected by laboratory tests including complete blood count, erythrocyte sedimentation rate, peripheral smear, urine analysis, electrolytes, liver, renal, and thyroid function tests, rheumatoid factor, ANA, anti-DNA, and antimitochondrial antibodies; nevertheless, a flu-like syndrome in six and nausea in three patients were noted at the beginning of the therapy.

IFNα has been used in the treatment of many diseases including the autoimmune diseases, rheumatoid arthritis, lupus erythematosus, and multiple sclerosis. However, Rönnblom *et al*[3] published that patients with malignant carcinoid tumours, especially when autoantibodies were present, could develop an autoimmune disease during treatment with IFNα. Furthermore, it has been reported that five patients developed myasthenic symptoms and AChR antibody positivity during IFNα treatment for malignancy and for HCV infection. Batocchi *et al*[4] supposed that IFNα could induce myasthenia gravis or simply manifest a preclinical disorder in two patients, one with bladder carcinoma and one with non-Hodgkin's lymphoma. Nevertheless, increased serum lactate concentrations, myopathic changes in EMG, and ragged red fibres in muscle biopsy that were compatible with mitochondrial myopathy raise some doubts about the diagnosis of myasthenia gravis in their first patients. Moreover, antibodies to AChR and myasthenia gravis are found occasionally in patients with motor neuron disease, epilepsy, other autoimmune diseases, aplastic anaemia, and acute lymphocytic leukaemia after bone marrow transplantation. IFNα down regulates mitochondrial gene expression within four hours with the maximal inhibition achieved at a concentration of 1000 u/ml, and mitochondrial dysfunction would be expected after 24–48 hours. Thus if the myopathy were related to IFNα, as Batocchi *et al* suggested, three months would be considered to be late. In addition, whether the serum concentration of IFNα was high enough to lead to this effect is unclear. D-Penicillamine induced myasthenia gravis and AChR antibody positivity disappears after the drug is discontinued and whether AChR antibodies persisting for two years without any symptomatology in a patient with malignancy could be attributed to IFNα treatment is debatable. In addition, autoimmunity associated with HCV is noteworthy, and activation of CD19/CD5 + cells, a subset of lymphocytes associated with human autoimmune disorders has been detected in more than half of the patients infected with HCV. Therefore, in the patient with HCV reported by Piccolo *et al*,[1] high dose IFNα could have induced myasthenia gravis, although their finding could be coincidental. Consequently, a possible contribution of underlying malignancy to myasthenic symptoms as well as certain clinical conditions that might lead to false positive AChR antibodies should be considered in patients with myasthenic symptoms induced by IFNα. We presume that IFNα may act through different mechanisms in myasthenia and in malignancy or HCV infection. Our impression, from a limited number of myasthenic patients, is that low dose IFNα is safe in myasthenia gravis and does not aggravate the disease.

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Habitual snoring, sleep apnoea, and stroke prevention

I read with interest the recent review articles on stroke prevention by Khaw[1] and Bronner *et al*[2] and was surprised that snoring and sleep apnoea were not mentioned as risk factors for stroke. Several cross sectional and case-control studies have shown that habitual snoring represents an independent risk factor for stroke, with odds ratios ranging from 2·1 to 3·3.[3] Based on a 10%–30% prevalence of habitual snoring and a 2%–4% prevalence of sleep apnoea[4] the risk of stroke associated with habitual snoring may be of the same magnitude as the risk associated with diabetes mellitus and dyslipidaemia.[5] The link between snoring and stroke seems to be particularly strong when habitual snoring is associated with symptoms or signs suggestive of sleep apnoea. In a study of 177 stroke victims and 177 age and sex matched controls, habitual snoring was found to be an independent risk factor for stroke with an odds ratio of 2·1.[6] The relative risk increased, however, to 8·0 in patients in whom habitual snoring was associated with a history of nocturnal apnoea, hypersomnia, and obesity. In a series of 59 patients with acute cerebrovascular events sleep apnoea was present in > 50%.[7]

Several physiological aberrations associated with obstructive apnoeas including hypoxaemia, cardiac arrhythmias, and pronounced variations in blood pressure and cerebral blood flow may contribute to the increased risk of stroke in patients with disordered sleep breathing.

Although it is not known if treatment of sleep apnoea reduces the risk of stroke, it seems to reduce vascular morbidity and mortality.[8 9] As sleep apnoea is a treatable condition, sleep apnoea and habitual snoring should be included in discussions of modifiable risk factors of stroke.

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The basis for behavioural disturbances in dementia

In her editorial, *The basis for behavioural disturbances in dementia*, Esiri reviews some possible neurochemical and pathological correlates of behavioural changes in dementia with particular reference to alterations in noradrenergic, serotonergic, and cholinergic transmission.[1] These data, offering some pathophysiological explanations for behavioural disorders in demented subjects are of great current interest but, unfortunately, this review is not complete and even presents some incorrect impressions that deserve the following comments:

Noradrenalin

Despite substantial neuronal loss in the noradrenergic locus coeruleus in Parkinson's and Alzheimer's diseases,[2 3] markers of noradrenalin metabolism in brain tissue are reported to be unchanged or increased.[1] A non-significant increase in Alzheimer type senile dementia has been reported by Yates *et al*,[4] whereas most other authors demonstrated significantly decreased noradrenalin values ranging from 29% to 52% of controls in the striatum, hypothalamus, and several cortical areas.[5–9] In non-cortical projection areas there was no evident decrease in noradrenalin concentration.[9]

On the other hand, Zubenko *et al*[10] found a specific and pronounced loss of noradrenaline in the middle frontal area, superior temporal cortex, and hippocampus (90% to 95%) in demented patients with major depression along with a relative preservation of choline acetyltransferase activity in several subcortical regions. These data in patients with Alzheimer's disease suggest that dysfunction of the noradrenergic system is also related to mental changes and depression in parkinsonian patients.[9]

Serotonin

Degeneration of serotoninergic systems in both Alzheimer's and Parkinson's disease results from neuronal losses in the dorsal raphe nuclei ranging in Alzheimer's disease from 10 to 76%, most severe in caudal parts containing many neurofibrillary tangles that may involve up to 90% of the neurons[2 11]; cell depletion in Parkinson's disease averages 20 to 40%.[12] This correlates well with a reduction of 5-HT and 5-HIAA in some cortical and hippocampal regions of Alzheimer disease brain ranging from 54% to 77%,[8] and a reduction of 5-HT, its

metabolites, and receptors in the striatum and medial frontal cortex.[13] These changes have been related to cognitive disorders and depression in patients with both these disorders.

Cholinergic system

Repeatedly reported shrinkage and depletion of cholinergic neurons in the magnocellular part of the basal nucleus of Meynert are accompanied by decreased choline acetyltransferase activity in the neocortex by 86% to 91%.[8] In Parkinson's disease, cell loss averages 30% to 40% without correlation with age or duration of illness, and is much higher in demented parkinsonian patients in whom it approaches the values in Alzheimer's disease (50% to 70%) than in non-demented patients (0% to 40%) who show neuronal losses only slightly higher than normal aged controls.[12] Even more severe depletion of the basal nucleus of Meynert with 75% to 80% loss or large cholinergic neurons has been found in Lewy body dementia[14] which correlates well with recent biochemical data.[1] The heterogeneity of degeneration of cholinergic neurons in the basal forebrain[15] and the variability in nucleus basalis cell depletion and loss of cholinergic markers in the neocortex and hippocampus, irrespective of cortical Lewy body or Alzheimer type pathology, suggest a primary degenerative process of the cholinergic forebrain system in Parkinson's disease, while secondary retrograde degeneration proposed for Alzheimer's disease has been confirmed by defective retrograde transport of nerve growth factor to the basal nucleus in the brains[16] of patients with Alzheimer's disease.

In conclusion, there are still some conflicting data on the neurochemical and pathological basis of behavioural changes in dementia disorders, the elucidation of which will be a major task for modern neurosciences.

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Esiri, in her editorial about behavioural disturbances in dementia[1] makes a common, and I believe important error in her classification scheme of behavioural abnormalities. She lumps apathy, withdrawal, and listlessness with tearfulness and "other manifestations of unhappiness" as part of "depressive behavioural disturbances". Actually her depressive category should be separated into two distinct categories: (1) *behaviour characterised by diminished activities and interactions often accompanied by slowness*. Apathy, increased inertia, and abulia are terms often used to describe diminished spontaneous behaviour, long latency in responding to queries and requests for action, and difficulty persevering with tasks. Many apathetic, abulic patients are not sad or unhappy or discouraged. Many have no associated mood abnormalities and most have little insight into their apathy. Lesions of the caudate nuclei, medial thalami, rostral brainstem tegmentum, and frontal lobes can cause such inert states. (2) *Mood abnormalities that include sadness, crying, discouragement, depression etc.*

True enough, many depressed patients have diminished activities but it is a great mistake to attribute all apathy, decreased activity, and inertia to depression. Apathy and diminished activities are a common presentation of caudate and thalamic infarcts, frontal lobe tumours, and progressive supranuclear palsy. The term "psychomotor retardation" is often used by psychiatrists to indicate depression, but the two conditions, apathy and depression, should be thought of as different phenomena that are often but not necessarily related.

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Esiri replies to Jellinger and Caplan:

I am grateful to Jellinger for adding supplementary information to that presented in my editorial. I was necessarily selective in such a condensed account of a complicated subject and largely limited my comments to findings that related to behavioural disturbances in dementia. I would emphasise the importance my colleagues and I attach to studying behavioural change prospectively and systematically. It is not clear that this was done in the study of noradrenalin by Zubenko *et al* that Jellinger refers to. Institutionalisation of patients that are studied may also lead to unintended bias—for example, when therapies have not been completely documented or are not fully taken into account as possible factors influencing neurochemical findings. The studies of the cholinergic system referred to by Jellinger, while of interest, have not specifically examined the relevance of cholinergic changes for behaviour in dementia, an area that certainly deserves attention.

The comments that Caplan makes about the desirability of subdividing my depressive category of behaviour into apathy and depressed mood, as reflected in evident unhappiness or crying, are well taken. I was intending only to indicate broad categories of behavioural change but agree that it is best to avoid assumptions about which individual types of behaviour go together, particularly in demented subjects who are often unable to give a direct account of subjective feelings. In searching for neurochemical correlates of behavioural change in dementia we have tried to avoid making assumptions about which types of behaviour are related, although analysis of detailed, prospectively acquired, data suggest that there are some constellations of symptoms that cluster together (T Hope, unpublished data).

I would agree that there are some conflicting data on the neurochemistry of behavioural change in dementia. In such a complex area of investigation it would be surprising if there were not. The important point is that prospective studies are being undertaken that are likely to resolve the differences and uncover new findings that have a direct bearing on the optimal way to manage the difficult behavioural problems that people with dementia suffer from.

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