tive sleep apnoea and they had also had sleep recordings to confirm the diagnosis. Snoring can be considered as a subocclusive stage of obstructive sleep apnoea but not all snorers develop it. It is possible that the muscles in the pharynx are affected in different ways during different stages of the disease.

In the specimens from all patients with obstructive sleep apnoea we found prominent neurogenic changes with signs of both denervation and reinnervation. In such cases we found analysis of the fibre type spectra to study fibre type adaption less relevant. Subtypes of fibre type II (a, b and c) were identified but showed a great variation and a further analysis was not considered necessary in the limited number of subjects.

Our morphometry did not show "a great variability of muscle fibre size" or atrophy as interpreted by Iannaccone *et al.* The fibre size distribution showed similar abnormalities in all patients, mostly with a two peak dispersion which is typical for a neurogenic lesion.

The muscle specimens were obtained during surgery from the same part of the cranial portion of the palatopharyngeal muscle in all patients and controls. The muscle was exposed after the tonsil had been removed. The same surgeon (HL) collected or supervised the collection of all specimens.

We consider our finding of a neurogenic lesion in the palatopharyngeal muscle in patients with obstructive sleep apnoea to be correct. The same type of lesions have been described by Woodson *et al.*⁵ in the uvular muscle of these patients. Recently we have published a study showing affected sensory pharyngeal nerves in obstructive sleep apnoea patients.⁶

We believe the different findings in the study by Iannaccone *et al.*¹ are due to a different biopsy site being examined and that the patients were not suffering from obstructive sleep apnoea. Whether the type of abnormalities described in the MPC muscle by Iannaccone *et al.* are present also in the palatopharyngeal or uvular muscle of snorers remains to be studied.

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N-Methyl-D-Aspartate (NMDA) antagonists in Parkinson's disease

We would like to comment on the letter by Montastruc *et al.*¹ in which negative results

in Parkinson's disease (PD) with the NMDA antagonist ifenprodil were reported. Ifenprodil acts at the polyamine binding site of the NMDA receptor. The authors state "this drug is, as far as we know, the sole NMDA antagonist currently available on the market", and "our study is the first to investigate the clinical effects of an NMDA antagonist in the treatment of PD".

The adamantanamines amantadine and memantine have been used since 1969 in the treatment of PD.²⁻⁴ The weak dopamine agonism in experimental studies seems insufficient to account for their clinical effects.^{4,5} It has been shown recently that amantadine and memantine act at the PCP binding site of the NMDA receptor-coupled ion-channel.^{4,6} It is therefore concluded that: 1) there are other NMDA antagonists clinically available besides ifenprodil and 2) NMDA antagonists have been used successfully for many years in the treatment of PD.

The disappointing results with ifenprodil do not therefore argue against the newly proposed "glutamate hypothesis" of PD,^{7,8} but may be related to: 1) the pharmacokinetic profile of the drug¹; 2) a rather weak influence of polyamine binding site antagonists compared with ion-channel blockers on NMDA receptor function or 3) a pathologically altered polyamine binding site in PD. These points have to be examined in future studies.

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Montastruc *et al.* reply:

We acknowledge Drs Kornhuber and Riederer's comments concerning our trial on ifenprodil in Parkinson's disease (PD).¹ We are well aware that the adamantanamines amantadine and memantine have anti-NMDA properties but amantadine is also known to release dopamine from striatal neurons, to inhibit the reuptake of dopamine and to have anticholinergic

effects.² Despite some experimental data, the respective role of these different pharmacological mechanisms remains unknown to explain the clinical anti-Parkinsonian properties of these drugs. Amantadine has only a weak and transient clinical anti-Parkinsonian efficacy which may be compatible with a weak dopamine effect. There are mainly speculative links between the anti-NMDA and the anti-Parkinsonian effects of amantadine. In our opinion, it is therefore still premature to support Kornhuber and Riederer, because of the amantadine and memantine data only, that "NMDA antagonists are used successfully for many years in the treatment of PD". This is why we were interested in investigating the clinical effects of another drug, such as, ifenprodil, which does not have dopamine effects.

It is perfectly clear, as we had already stated in our first letter,¹ that "our work does not exclude a definite role for NMDA antagonists in PD" because of the negative ifenprodil data. We had also already written that other NMDA antagonists with better pharmacodynamic or pharmacokinetic profile may be effective.¹ Since our results have been published, we know that there is another NMDA antagonist which is available in clinical practice. A recent open study has suggested that dextromethorphan, an antitussive drug that is also a non competitive antagonist of the NMDA receptor, might have some efficacy in PD.³

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Risk of stroke in TIAs with a cerebral infarct on CT

I have read the article by Koudstaal *et al.*¹ in which the authors find a relevant ischaemic lesion on CT in 13% of TIAs, 35% of RINDs and 49% of minor stroke. In their wide bibliographic review they only mention one comparative study on infarction characteristics between patients with transient and persisting signs.² We reported four years ago similar results in 219 patients with reversible ischaemic attacks demonstrating that the frequency of brain infarction was related to the duration of the neurological deficit.³ Ischaemic lesions on CT closely correlated with abnormalities on supra-aortic trunk angiography or Doppler ultrasonography. A higher percentage of recurrence was found in those patients with infarctions, but the difference was not significant.

Koudstaal *et al.* mentioned the possibility of an increased risk of major stroke in TIAs with cerebral infarct on CT.¹ Using our pre-

vious data, we have performed a Cox multivariate analysis of the probability of survival without stroke in 92 TIA patients with normal CT scan and in 24 TIA patients with cerebral infarct, followed during an average period of 21 months. Age, carotid lesions detected by ultrasonographic examination or angiography, and glycaemia level higher than 100 mg/dl were used as covariates since in a previous study we observed that these variables were related independently with the prognosis.⁴ Ninety nine per cent of the TIAs without infarct and 79% of the TIAs with infarct survived without suffering a major stroke (Mantel-Cox test, $p < 0.0001$). The probability of survival, free of stroke, was related with the presence of carotid atherosclerosis (odds ratio = 3.07, 95% confidence intervals = 1.27–7.40). Ischaemic lesions in the CT scan, age and glycaemia levels had no independent predictive value.

Our results suggest TIAs with cerebral infarct have a poorer outcome due to a higher frequency of atherosclerosis of the neck arteries.

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Koudstaal and van Gijn reply:

We would like to thank Dr Dávalos *et al* for their comments on our study.¹ Their observation of a higher risk of stroke in TIA patients with a cerebral infarct on CT in a univariate, but not in a multivariate analysis, is very interesting.² We have recently completed a study of predictors of major vascular events in 3150 patients with a TIA or minor stroke who were entered into the Dutch TIA Study.³ In contrast to the findings of Dr Dávalos *et al*, we found that ischaemic abnormalities on CT scan were an independent risk factor for stroke and other vascular events, irrespective of the duration of the symptoms. In this multicentre study, however, it was impossible to collect objective information on the presence and degree of atherosclerotic abnormalities of the extracranial bloodvessels, which may explain the discrepancy between our findings and those of our Spanish colleagues.

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Diabetes and stress hyperglycaemia in stroke

Kiers *et al*¹ presented a prospective study on 176 stroke patients focused on stroke outcome in relation to hyperglycaemia and diabetes.¹ The patients were divided into four groups: 1) normoglycaemic patients with normal or marginally elevated glycosylated haemoglobin (HbA1c) level, without history of diabetes; 2) hyperglycaemic patients with normal HbA1c, without history of diabetes ("stress hyperglycaemia"); 3) new diabetics (hyperglycaemic patients with elevated HbA1c level, without history of diabetes) and 4) known diabetics. Stroke severity on admission was significantly worse in the patients with stress hyperglycaemia and in the known diabetics than in their normoglycaemic counterparts. In addition, hospital mortality was higher in the patients with stress hyperglycaemia, in the newly-diagnosed diabetics, and known diabetics compared with the normoglycaemic patients.

One of the conclusions was that there exists a relationship between diabetes and poor stroke outcome. This conclusion is hardly justified. It has been shown that reactive or "stress" hyperglycaemia is associated with poor stroke outcome in non-diabetics.^{2,3} In fact, this is one of the results of the authors as well. However, incorrect conclusions are readily made when diabetics are compared with non-diabetics after exclusion of the non-diabetics with stress hyperglycaemia. It is very probable that new or known diabetics with acute stroke cannot escape acute stress and reactive hyperglycaemia either. In one study, taking this aspect into consideration, in-hospital case fatality rate was 35% in diabetics with reactive hyperglycaemia but 0% without reactive hyperglycaemia.² When grouping the patients of Kiers *et al*¹ by HbA1c level, the case fatality rate (95% confidence interval) was 19.1% (11.0–27.2) for the 89 patients with normal HbA1c and 26.3% (14.9–37.7) for the 57 patients with elevated HbA1c. At present, studies based on HbA1c measurements suggest that no association exists between diabetes and poor short term (3 months) outcome in stroke.⁴ For Kiers *et al* point out that several animal studies have shown that hyperglycaemia increases ischaemic brain damage. However, in some studies of experimental cerebral ischaemia hyperglycaemia has been neuroprotective.^{5,6}

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Kiers, Davis, Larkins *et al* reply:

We thank Drs Murros and Fogelholm for their comments. The relationships between diabetes, stress hyperglycaemia and stroke outcome are indeed complex. In our study design, we attempted to examine separately the effects of diabetes and stress hyperglycaemia on stroke outcome, compared with the euglycaemic non-diabetic state, using the four groups categorised on the basis of history, fasting glucose and glycosylated haemoglobin.¹ We acknowledge that stress hyperglycaemia was also likely to be present in some of the diabetic patients, but these subjects could not be identified.

Our study¹ demonstrated significantly higher mortality in the combined diabetes groups (as well as the stress hyperglycaemia group) compared with the euglycaemic, non-diabetic subjects, but we would agree that this adverse effect could have been due to stress hyperglycaemia in a proportion of the diabetic patients.

We are aware that there have been animal studies of cerebral ischaemia which have suggested that hyperglycaemia may be protective,^{2,3} but there is also substantial evidence to the contrary.^{4,5} What has been clearly shown by the results of our study, and previous human investigations,^{6,7} is that elevated blood glucose is associated with a worse outcome after stroke. This association was even present within our euglycaemic group. As discussed in our paper, it is not possible to conclude whether this is a causal relationship or whether the degree of hyperglycaemia reflects the severity of the acute event. Until the mechanism of the association can be resolved, however, glucose infusions should be avoided in acute stroke.⁸

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