deamination and auto-oxidation. It has been suggested that selegiline reduces oxidative stress and thus might be beneficial in parkinsonism.

Catechols, including dopamine and levodopa, are known to be cytotoxic. We have investigated whether selegiline protects neurones against toxicity induced by dopamine or levodopa in SH-SY5Y catecholaminergic neuroblastoma cells. We found that in fact selegiline exacerbated the toxicity induced by dopamine, even though selegiline itself at a concentration as high as 100 $\mu\text{mol/l}$ was without effect (C T Lai and P H Yu, 6th international amine oxidase workshop, Saskatoon, Canada, 1994). This exacerbation of toxicity was dose dependent with respect to both dopamine and selegiline. As little as 0.1 μmol selegiline/l caused a small but significant increase in toxicity induced by dopamine. Although levodopa is as toxic as dopamine towards SH-SY5Y cells, selegiline did not exacerbate its toxicity. Structural analogues of selegiline such as 4-methylselegiline, one of its metabolites ((-)-N-methylamphetamine), and a monoamine oxidase A inhibitor (clorgyline) also exacerbated toxic effects induced by dopamine.

These observations suggest that selegiline may be toxic in vivo towards certain cells when dopamine concentrations are increased, and this might be relevant to the increased mortality seen in patients with Parkinson's disease treated with selegiline and levodopa combined. Although the neuroprotective effect of selegiline has been questioned, the drug seems to offer symptomatic relief to patients with Parkinson's and Alzheimer's diseases, and it exhibits neurorescue effects in several animal models.² Some new, specific, irreversible monoamine oxidase B inhibitors, the aliphatic propargylamines,³ which rescue neurones in several in vivo systems, do not exacerbate toxicity induced by dopamine in the above SH-SY5Y system. These compounds could be a useful alternative chemotherapy, offering both symptomatic benefit and neuroprotective and rescue properties without toxicity.

P H YU*
Professor
C T LAI
Postdoctoral fellow
A A BOULTON*
Professor

Neuropsychiatry Research Unit,
Department of Psychiatry,
University of Saskatchewan,
Saskatoon,
Saskatchewan,
Canada S7N 5E4

*P H Yu and A A Boulton are two of the authors of patents on the aliphatic propargylamines held by the University of Saskatchewan.

- 1 Lees AJ on behalf of the Parkinson's Disease Research Group of the United Kingdom. Comparison of therapeutic effects and mortality data of levodopa and levodopa combined with selegiline in patients with early, mild Parkinson's disease. *BMJ* 1995;311:1602-7. (16 December.)
- 2 Yu PH, Davis BA, Zuo DM, Zhang X, Fang J, Lai CT, et al. Neurochemical, neuroprotective and neurorescue effects of 2-hexyl N-methylpropargylamine (2-HxMP), a new MAO-B inhibitor without amphetamine-like properties. *Prog Brain Res* 1995;106:113-21.
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"On treatment" rather than intention to treat analysis should have been used

EDITOR,—On the basis of intention to treat analysis the Parkinson's Disease Research Group of the United Kingdom concludes that mortality was significantly higher with combination treatment of levodopa and selegiline (arm 2) than with levodopa alone (arm 1).¹ This conclusion, however, is not justified, for several reasons.

Firstly, the main measures of the outcome of treatment were (a) serial assessments of disability, (b) the frequency and severity of adverse events,

and (c) deaths from all causes. The difference in mortality between arms 1 and 2 was compared with the log rank test, and the difference in survival between the arms was significant. For a confirmatory assessment of the difference in mortality between these arms, however, the reported P values need to be adjusted according to the value of α . Further adjustments to the value of α need to be made because the reported P values were the result of (at least) a second interim analysis and of three comparisons (arm 1 with arm 2, arm 1 with arm 3, and arm 2 with arm 3).

Secondly, although adjustments for age, sex, and other baseline prognostic factors were performed with the Cox proportional hazards model, the group did not test further relevant prognostic clinical factors, such as the duration of pre-treatment, concomitant diseases (for example, cardiovascular diseases, diabetes mellitus, bronchopulmonary diseases), and concomitant treatment unrelated to Parkinson's disease. Such factors, however, may affect mortality.

Finally, 51.8% of the patients were withdrawn from arm 1 but only 45.4% from arm 2. It is unclear, however, what treatment most of these patients were taking at the time of death. To determine whether the excess mortality in arm 2 was really an effect of treatment the mortality has to be analysed by an "on treatment" approach rather than by the intention to treat analysis used. Although this was in fact done and the ratio of the mortality in arm 2 to that in arm 1 was similar to that obtained with the intention to treat analysis, the research group does not state whether the difference was significant. As can be approximated from the 95% confidence interval, the difference in mortality was not significant.

M GERLACH
Privatdozent

Clinical Neurochemistry,
Hospital of Psychiatry,
University of Würzburg,
D-97080 Würzburg,
Germany

P RIEDERER
Professor

Institute for Applied Mathematics and Statistics,
University of Würzburg,
D-97070 Würzburg,
Germany

H VOGT
Professor

- 1 Lees AJ on behalf of the Parkinson's Disease Research Group of the United Kingdom. Comparison of therapeutic effects and mortality data of levodopa and levodopa combined with selegiline in patients with early, mild Parkinson's disease. *BMJ* 1995;311:1602-7. (16 December.)

Causes of death need confirmation

EDITOR,—After 5.4 years of follow up the Parkinson's Disease Research Group reports a significantly higher mortality in patients with early, mild Parkinson's disease given levodopa plus selegiline (arm 2) than in those given levodopa alone (arm 1). Although the causes of the 60% increased mortality "remain to be elucidated," the group concludes that the data "cast doubts on the chronic use of selegiline."¹ This conclusion seems conjectural.

Firstly, the suggested deleterious effects of selegiline on the cardiovascular system are disproved by the fact that deaths due to heart or cardiovascular disease were not increased in arm 2. However, baseline data did not include data on cardiovascular and other concomitant diseases, which are present in about half of patients with Parkinson's disease² and are a major factor in outcome.

Secondly, significant differences in the cause of death were due to Parkinson's disease being 3.5 times more commonly cited as a cause in arm 2. Causes of death, however, were based only on entries in death certificates, the reliability of which remains debatable,³ and "postmortem confirmation . . . was available only in a small number of cases." While the clinical diagnosis had

to be revised in 6.1% of patients in the study, four studies have shown that only 76-84% of patients with clinically diagnosed Parkinson's disease had this disorder at necropsy.⁴

Thirdly, most patients with Parkinson's disease die of secondary or coincidental disorders.^{2,5} This is confirmed by a personal necropsy series of 600 patients with the disease (505 with confirmed Parkinson's disease of Lewy body type): under 2% died of akinetic or hyperthermic states in late stages of illness.

Fourthly, the mortality data in the research group's study are at variance with those in 10 previous long term trials of selegiline in Parkinson's disease: among 2047 patients (959 given selegiline, 1088 controls) there were 58 deaths, two occurring months after selegiline was stopped.⁶ The mortality was 2.7% in the selegiline group (2.5% excluding the two late deaths) and 2.9% in the control group ($P=0.7$). Causes of death were heart and embolic diseases, neoplasms, etc; Parkinson's disease was never mentioned. Hence the causes of death in the research group's study need further confirmation.

From an ethical viewpoint I do not understand why the trial continued after the analysis in December 1994 (one year before publication) showed significant differences in mortality between arms 1 and 2—a result that brought other studies to a premature end.²

K A JELLINGER
Director

Ludwig Boltzmann Institute of Clinical Neurobiology,
Lainz-Hospital,
A-1130 Vienna,
Austria

- 1 Lees AJ on behalf of the Parkinson's Disease Research of the United Kingdom. Comparison of therapeutic effects and mortality data of levodopa and levodopa combined with selegiline in patients with early, mild Parkinson's disease. *BMJ* 1995;311:1602-7. (16 December.)
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Authors' reply

EDITOR,—We emphasised that a causal relation between long term selegiline (10 mg/day) and the increased mortality in arm 2 of our trial (levodopa plus selegiline) had not been established. The meta-analysis done by Orion combined trials of selegiline alone with those of combination treatment and is therefore not directly comparable. Even so, the calculated mortality odds ratio for studies with more than 3.5 years of follow up is 0.94 (95% confidence interval 0.55 to 1.61) and is compatible with our results.

Our trial does not exclude the possibility that selegiline may have mild neuroprotective effects but questions its clinical relevance. We also failed to find important advantages for combination treatment with respect to dyskinesias and motor fluctuations. Longer follow up of a cohort by the United States Parkinson Study Group has come to similar findings.¹ After careful deliberation we decided that all patients receiving selegiline in the trial should be notified of the results before publication and, as a precaution, advised to withdraw selegiline. The results of the withdrawal of selegiline and its effect on disability and subsequent requirements of levodopa, with mortality to December 1994, will be available in six months' time.

C Warren Olanow and colleagues comment that the number of deaths in our study is extremely