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.

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

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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.

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- 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

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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

high; the standard mortality ratio was 1.42, which is much lower than that in recently published community based studies (one British,² one American³) and similar to that in hospital based series after six years' treatment with levodopa.⁴ Olanow and colleagues also state that the dose of levodopa was fixed in arm 2 and not adjusted to clinical need; if they read our paper's patients and methods section they will see that the dose in both arms of the trial was regulated to obtain optimum improvement.

Mark T Silva and colleagues comment on the causes of death listed in table 3. Inaccuracy of death certificates is well recognised and presents particular problems in elderly people. All entries on the death certificates were coded from the *International Classification of Diseases* (ninth revision), and causes of death were coded according to the World Health Organisation's rule 3 for determining cause of death. For example, if bronchopneumonia was the sole entry in part I of the certificate and Parkinson's disease was mentioned in part II, Parkinson's disease was coded as the cause of death.

As M Gerlach and colleagues indicate, the "on treatment" hazard ratio (1.44) was not significant, but the magnitude of difference was similar to that obtained with the intention to treat analysis. Altogether 60% of the deaths occurred while patients were still in the treatment group to which they had initially been randomised. The interim analyses were carried out annually; a nominal level of significance ($P < 0.005$) was used, which maintained the overall level of significance ($P < 0.05$), assuming a maximum of 10 interim analyses. Between April 1995, when investigators were notified of the findings, and submission of the paper for publication we received additional information on patients, and reanalysis (with these new data included) altered the P value. We would emphasise that all patients' records were flagged at the NHS Central Register. In addition, most of the survivors were seen in 1994, and those lost to follow up were relatively few and equal in the two arms.

As in any other trial, an imbalance between treatment groups in an unrecorded characteristic at baseline may have occurred. The fundamental strength of randomised trials is that both known and unknown confounders are balanced across interventions. Olanow and colleagues and K A Jellinger raise the issue of misdiagnosis. The diagnosis was revised in only 6% of cases in arms 1 and 2, and on the basis of clinicopathological studies probably as many as a fifth of the patients who died would have failed to fulfil confirmatory pathological criteria for Parkinson's disease.⁵ This difficulty, however, reflects the reality of clinical practice. For misdiagnoses to explain our findings the imbalance between the two arms would have to be great. We have calculated that to replicate the number of deaths in arm 2 it would be necessary for 60-89% of patients to have been misdiagnosed, assuming a twofold to threefold relative mortality for these patients compared with those with Parkinson's disease.

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Compliance with infection control procedures in dentistry

EDITOR,—Infection control should be adequately taught and carefully monitored in dental and medical schools.¹ Little objective evidence exists on how compliant dental staff are in undertaking infection control measures. We previously reported that the compliance of British hospital dental staff and students was inadequate: protective gloves were often neither changed nor washed between patients.^{2,3} Only half of staff and students wore protective eyewear, and only about a third wore a face mask. As a result of those observations, infection control procedures were re-emphasised.

Four years later, over a period of five weeks, we observed the compliance of dentists and dental students working in the same primary dental care clinic of the dental hospital. We used a video camera mounted on the ceiling. The camera had been installed two weeks previously, and the staff and students were unaware of its purpose or precisely when it was operating. Procedures were recorded on videotape and later assessed by two clinicians. A total of 215 contacts between patients and the dentists and students were scrutinised, consisting of 114 examinations (79 undertaken by dentists and 35 by dental students) and 101 treatment procedures (71 by dentists and 30 by dental students). The treatments were all surgical or restorative dentistry likely to produce aerosols or splatter. Compliance with hand washing before and after contact with the patient and the use of gloves, face masks, and eye protection were recorded. Other infection control procedures, such as sterilisation of instruments, were not assessed.

We found that the health care workers washed their hands before donning gloves in only 23% of contacts, did not wear gloves in 13%, and changed gloves between patients in only 56% (table 1). They wore face masks during only 82 contacts and protective eyewear in only 62. These observations were similar to those in our previous studies, except that more staff and students were now changing gloves or washing hands between patients.

Thus, even when provided with training and all suitable protective wear, neither hospital dentists nor dental students comply completely with infection control procedures. Indeed, compliance has not greatly improved over the past four years despite additional education of dental staff and students³ and the increasing prevalence of HIV infection and hepatitis C in the general population. The attitudes of dental staff and students to infection control procedures clearly require improvement, but whether additional or modified education measures alone will suffice is unclear. Perhaps legal methods may be the only means

of ensuring adequate compliance with infection control.⁴

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Tobacco advertising

Cigarette advertisements are still allowed on television in Japan

EDITOR,—Bruce Guthrie says that if the British government is serious about reducing smoking it should ban tobacco advertising.¹ I am embarrassed to say that cigarette advertising has not yet been banned from television in Japan. Young people, especially teenage girls, tend to think that smoking is glamorous and fashionable. The increase in the number of young women who smoke is one of Japan's most important problems.² According to the Japan Tobacco Corporation, the prevalence of smoking among women aged 20-29 was 16.6% in 1985 and had risen to 19.5% in 1990.³

According to a survey conducted in 1995, the prevalence of smoking among women in their 20s was 23.3%. The survey also showed that the prevalence of smoking was 58.8% among men and 15.2% among women—in other words, about 27.3 million men and 7.5 million women smoke in Japan. The number of female smokers was the highest since the Japan Tobacco Corporation began its surveys in 1965. Although a total ban on all tobacco advertising may be difficult, the Japanese government should prohibit cigarette advertising on television by law to indicate that it is taking the people's health and future seriously.

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Committee exists to monitor agreements on tobacco advertising

EDITOR,—I read with concern the letter from Bruce Guthrie reporting his survey of poster advertisements for tobacco near schools.¹ Guthrie does not make any mention of the Committee for Monitoring Agreements on Tobacco Advertising

Table 1—Hand washing and use of gloves by dentists and dental students during contact with patients. Figures are numbers (percentages) of contacts

	Examinations		Treatments	
	Dentists (n=79)	Dental students (n=35)	Dentists (n=71)	Dental students (n=30)
Hands washed before gloves put on	11 (14)	9 (26)	9 (13)	21 (70)
Gloves worn	64 (81)	29 (83)	64 (90)	30 (100)
Gloves changed between patients	50 (63)	7 (20)	45 (63)	18 (60)
Gloves neither changed nor washed between patients	5 (5)	0	8 (11)	1 (3)