MRC Fluphenazine Maintenance Trial in Schizophrenia

DEAR SIR,

It is widely recognised that long-term neuroleptic treatment can cause tardive dyskinesia. This syndrome is thought to be due to hypersensitivity of nigrostriatal dopamine receptors. It has been suggested (Davis & Rosenberg, 1979) that an analogous syndrome of tardive psychosis might be caused by supersensitivity of mesolimbic dopamine receptors following long-term neuroleptic treatment. This syndrome, like tardive dyskinesia, could be apparent during drug treatment but would become more obvious after withdrawing drugs. Patients alleged to have this syndrome have been described clinically (Chouinard & Jones, 1980).

Curson *et al* (*Journal*, May 1985, 146 474–480) in their follow-up study of the MRC fluphenazine maintenance trial in schizophrenia reported the unexpected finding that patients who had spent the greatest percentage of their time taking neuroleptic drugs had the highest relapse rate. In a recent statistical overview of clinical trials of maintenance therapy with fluphenazine, Tiecher & Baldessarini (1985) suggested that doses of the order of 50 mg fortnightly are "antitherapeutic" for 50% of patients, and that much lower doses are more effective. Both of these observations are consistent with the hypothesis that high exposure to fluphenazine causes tardive psychosis in some patients. The great majority of patients included in placebo-controlled studies of long-term neuroleptic treatment, including those in the MRC study, had received neuroleptic drugs before entering the trial. Some of these patients could have developed tardive psychosis even before entering the studies.

Whilst the existence of tardive psychosis is not yet definitely proven, it is clearly a possibility which should be kept in mind in the interpretation of research studies of maintenance neuroleptic treatment.

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Macrocytosis and Cognitive Decline in Down's Syndrome

DEAR SIR,

In a retrospective longitudinal study of ageing in Down's syndrome, we reported earlier that significant cognitive decline, as determined by Stanford-Binet testing, was present in 39% of 23 Down's syndrome residents over the age of 50 years (Hewitt *et al*, 1985). This cognitive decline was significantly associated with decreased visual acuity, hearing loss and macrocytosis. In order to examine further the relationship between cognitive decline and macrocytosis the case records of the 23 subjects were reviewed and their mean corpuscular volumes (MCVs), over time noted. As a result 121 MCV readings were obtained. The relationship between the MCV readings and the subjects' base-line mental age (MA) assessments were then analysed.

In one case without intellectual deterioration MCVs were not available and this patient was excluded from further analyses. In two cases only one MCV had been obtained. For the remainder, the mean number of MCV readings was 5.9 (range 2 to 18). In 20 cases, the mean MCV was calculated for each individual and used for statistical purposes; in two cases the single MCV reading was entered into the analysis.

In general, MCV readings had been obtained later in the patients' lives than the MA scores. It was therefore not possible to investigate directly whether there was an inverse relationship over time between MCV and MA. However, mean MCV for those with intellectual deterioration was 100.23 fentolitres (range 92 to 106) compared with 95.14 fentolitres (range 91 to 103.2) for those without intellectual deterioration. This difference was significant ($t=2.9970$, 20 d.f., $P<0.005$). Closer inspection revealed that intellectually deteriorated patients were older when their first MCV reading was obtained. Mean chronological age at first MCV reading for deteriorated patients was 50.6 years compared with 42.7 years for non-deteriorators, ($t=2.5858$, 20 d.f., $P<0.01$). For the entire group, however, the most recent MCV was not larger than the earliest MCV ($t=1.0969$, 19 d.f., NS) suggesting that advanced age is not associated with raised MCV in Down's syndrome. A final check on the finding that MCVs for intellectually deteriorated patients are higher than for those without intellectual deterioration was made by analysing only those MCVs obtained beyond the patient's fiftieth birthday. Mean MCV for deteriorations now became 100.65 fentolitres (range 92 to 109.6) and 96.5 fentolitres (range 92.4 to 100.5) for non-deteriorators.

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