EFFECTS OF NEUROLEPTIC DRUGS ON MAO ACTIVITY

DEAR SIR,

The article "Platelet Monoamine Oxidase Activity in Acute Schizophrenia" (*Journal*, July 1981, **139**, 16–22) suggests that the effects of neuroleptic drugs (on platelet MAO activity) may explain previous reports of low platelet MAO in schizophrenia. Genetic control of platelet MAO has been established by a number of twin studies, (Nies *et al*, 1973; Winter *et al*, 1978; Hussein *et al*, 1980). Moreover, studies of schizophrenic twins including those discordant for schizophrenia (Wyatt *et al*, 1973; Koide *et al*, 1981) confirm the genetic effect, though not always showing lower mean values for the schizophrenics (Koide *et al*, 1981).

We have been systematically collecting blood from a series of schizophrenic and control twins during the course of another study. We have established zygosity by blood grouping in all cases, and have harvested platelets for MAO activity. The findings from Owen and his colleagues prompted us to examine the eight monozygotic twin pairs who are discordant for schizophrenia (and hence discordant for neuroleptic ingestion) that we have examined so far.

Seven probands were diagnosed as schizophrenic and one as schizoaffective psychosis by SADS interview (Spitzer and Endicott, 1975). Seven were taking neuroleptic agents at the time blood was drawn for platelet MAO; six had been doing so chronically for over 5 years, and one intermittently including continuous administration over the three weeks prior to MAO estimation (range: chlorpromazine equivalent 100 mg to 1200 mg per day). The remaining proband had had a course of stelazine four years previously and was therefore excluded from the present analysis. None of the co-twins had ever received neuroleptics nor been treated for any psychiatric condition. One co-twin and one proband (from different pairs) were epileptic. Comparative data were obtained from a sample of non-psychiatric volunteer twins, age and sex matched to the schizophrenics.

Platelet MAO was prepared and analysed using ^{14}C tyramine as substrate (method similar to that of Owen *et al* with the exception that activity is expressed per 30 mins. and therefore all our values should be doubled before a direct comparison is made with their results, Reveley, 1980).

As Table I shows we found mean platelet MAO activity to be significantly lower ($t = 2.56$, $P < .02$) in the seven twin pairs which included a schizophrenic, than in age and sex matched controls twin pairs. Examining intrapair differences in the twins discordant for schizophrenia and neuroleptic ingestion, we found that the mean platelet MAO activity was identical, (matched pair $t = .004$) and the correlation between values very high, (.84, Table II). The degree of genetic influence, or heritability of a continuously variable trait such as MAO activity can be roughly estimated by calculating the interpair and intrapair variances, and then the intraclass correlation:

TABLE I

Mean platelet MAO activity

	nm/mg protein/30 mins.
Schizophrenic twins taking neuroleptics (n = 7)	13.45±6.32
Non schizophrenic, nonmedicated cotwin (n = 7)	13.45±8.41*
Normal age- and sex-matched control twins (n = 14)	19.09±4.11†

* Matched pairs $t = -.004$ ns.
† $t = 2.56$ $P < .02$.

TABLE II

Intrapair differences in the discordant twins

	nm/mg protein/30 mins.
Mean intrapair difference in platelet MAO activity	3.68±2.9
Intraclass correlation r = 0.84*	
Heritability $h^2 = 84\%$	

* $P < .02$.

$$\frac{\text{interpair variance} - \text{intrapair variance}}{\text{interpair variance} + \text{intrapair variance}} = \text{intraclass correlation, r}$$

The heritability is then r × degree of relationship, (for MZ twins with identical genes the degree of relationship is one) so for this sample the genetic influence on MAO activity is 84 per cent.

Thus in our discordant twin pairs MAO activity appears to be independent of schizophrenic illness and neuroleptic ingestion, and is also significantly lower than that obtained from normal twins. We are continuing to collect cases and would warmly welcome

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the chance to examine schizophrenia discordant MZ twins from other centres for this and other asepcts of our study.

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RESEARCH DIAGNOSTIC CRITERIA FOR PRIMARY AFFECTIVE DISORDER

DEAR SIR,

The St Louis Criteria (Feighner *et al*, 1972) and the Research Diagnostic Criteria (Spitzer *et al*, 1978), although widely used in research on depression, have been recently criticized. It has been stressed that this diagnostic approach does not provide homogeneous groups (Nelson *et al*, 1978; Feinberg *et al*, 1979; Nelson and Charney, 1980).

One classical way to test the consistency of a nosological grouping is to follow the course of the disease over time.

Therefore a sample of patients previously diagnosed as having a primary affective disorder (PAD) has been followed up for a period of four years. One hundred and fourteen patients that met the criteria for definite PAD (and also meeting the diagnosis of major depressive disorder, primary subtype) were hospitalized at the Department of Clinical Psychiatry of the University of Florence during the years 1975–6. Seventy-eight cases out of the total were subsequently followed up as out-patients for at least 4 years; at the end of this period new assessments, on the basis of the newly acquired knowledge, were made by experienced psychiatrists not informed about the earlier diagnoses. The inter-diagnoser agreement was satisfactory ($k = .92$, $n = 44$).

The diagnoses of 63 patients (80.8 per cent) were still consistent with the former ones: 25 patients relapsed into episodes again diagnosable as PAD, whilst 38 had a four year period of well-being. Conversely 15 cases (19.2 per cent) had subsequent diagnoses other than affective: 7 patients showed paranoid symptoms, 7 had clearly hysterical signs, and one became an alcoholic.

Whether further diagnoses of schizophrenia, hysteria or alcoholism are compatible with that of affective disorder, depends on one's view of the natural history of such a disease. In fact it is still controversial whether a patient suffering from a major psychiatric disorder, such as depression, can recover and then be affected by a different major psychopathy, e.g. schizophrenia. However, most biological or psychological theories of depression assume that this disorder is incompatible with non-affective states. In any case, as the RDC are aimed to select homogeneous groups for research purposes, the exclusion of false negatives ought to be preferred to the inclusion of false positives. Thus, diagnoses changing over time have to be seen as at least dubious. Indeed it appears reasonable that some depressive onsets of schizophrenia, some affective signs superimposed onto hysterical personalities, or other secondary dysthymias, may be misdiagnosed as PAD.

This lack of homogeneity is not surprising if one considers that the RDC are mere checklists of symptoms, which ignore other sources of clinical knowledge, such as premorbid personality, family history, physiopathological markers, longitudinal course of the illness, etc. These factors have been the basis of the clinical method and nosology since Sydenham onwards.

In my opinion, therefore, the RDC, although helpful for improving standardization and diagnostic agreement, still fail to provide homogeneous samples.