consistent with Hamp's (1961) work with normal individuals who displayed evening mood elevation. Perhaps such diurnal variation is more widespread than an occurrence in endogenous depressives.

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CONTINUED NEED FOR PLACEBOS

DEAR SIR,

The superiority of imipramine over placebo has been clearly demonstrated by Drs Rogers and Clay (*Journal*, December 1975, **127**, pp 599–603) though there are at least two simpler methods of drawing the same conclusion about efficacy: via the overall response rates and via the trends of individual trials.

In their summary, however, the authors state that further drug-placebo trials in non-institutionalized patients with endogenous depression are not justified. This is not so. It is more ethical to use placebo as a control than imipramine.

Consider a new drug which has gone through an exhaustive series of uncontrolled trials from which it could reasonably be expected that 70 per cent of such patients will show a 'greatly or moderately improved' response. The therapeutic benefit is not yet confirmed; there is reasonable doubt and some sort of quantitative evaluation is desirable and justified. A controlled trial is needed. But which control—imipramine or placebo?

Sixty-five per cent of the imipramine patients can be expected to respond adequately (the authors have shown), contrasted with 70 per cent of patients on the new drug. To reach a statistically significant result at the 0·05 level will require a trial with 1,000 patients if the original premise is correct. Five hundred patients will receive imipramine, of whom 65 per cent can be expected to respond and 35 per cent not to do so. Thus 175 patients on the control treatment can be expected to show an inadequate response.

If, on the other hand, a placebo control were to be used with a response rate of say 30 per cent (the first 14 trials in their Table I gave a response rate of ·32 with a standard deviation of ·19) then the controlled trial with the new drug will require about 30 patients. Of these, 15 will be on placebo and 10 of these can be expected to show an unsatisfactory response.

I have no difficulty in justifying the continued use of placebo, even though the value of imipramine is beyond dispute.

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SCHIZOPHRENICS' FAMILIES

DEAR SIR,

Fowler and Tsuang (*Journal*, January 1976, pp 100–1) take issue with our finding (*Journal*, August 1975, **127**, pp 97–108) of more personality disorder in the families of our schizophrenic probands than in the controls. In fact there does not appear to be any substantial point of disagreement between our data and those of Fowler and Tsuang, but rather a difference of terminology. Those relatives whom we regarded as suffering from the kinds of personality disorder which our analyses suggested were biologically akin to schizophrenia they would have called cases of 'suspected schizophrenia'. Those illnesses which we did not think were biologically related to schizophrenia they found in their families to be 'transmitted independently of schizophrenia'. In our study this applied to affective disorders, neurotic reactions (except possibly in females) and neurotic personality disorders, subnormality and suicidal behaviour, while Fowler and Tsuang mention particularly affective disorder and alcoholism. As regards the latter, some but not all of our cases were thought to have arisen on the basis of personality disorder of the kind related to schizophrenia, while Fowler and Tsuang emphasize that 'alcoholism and some personality disorders in the families of

schizophrenics are more a function of a selective mating of the schizophrenic parent(s) than a biological variant of schizophrenia'.

We would not dissent from this point of view, except for a reservation about terms. For instance, analysis of our data led us away from the monogenic hypothesis of schizophrenia and its spectrum, which might have justified calling all the cases, whether overtly psychotic or not, 'schizophrenic'. Instead, there was a complex situation in which transmission of schizophrenia and its related conditions appeared more likely to be polygenic. In addition, environmental factors, and, as we pointed out in our second paper (*Journal*, August 1975, **127**, pp 109–18), assortative mating on a phenotypic basis, that is between disturbed, unstable or disadvantaged individuals not necessarily of the same genotype, seem to play an important part in determining the types of abnormality manifested by the sibs of probands.

The low rate of schizophrenia among our parents —1 in 146—is not exceptional, and similar rates have been reported by Hallgren and Sjögren (1959) and by Kay and Lindelius (1970). However, differences in diagnostic criteria obviously enter the picture here. Should 'schizophrenia' be reserved only for those individuals who show certain defined psychotic symptoms, as proposed, for example, by Wing *et al* (1974); or should the conditions which Rosenthal and Kety (1968), for instance, considered to be part of the spectrum, such as suspected chronic schizophrenia and markedly inadequate personalities be included?

Our view is that in the present state of knowledge about aetiology, the former procedure is to be preferred. This would leave the question of the definition and nature of the less well-defined conditions open to further investigation and avoid closing the issue prematurely.

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SULTHIAME IN THE MANAGEMENT OF PSYCHIATRIC PATIENTS

DEAR SIR,

Until recently, sulthiame has been primarily investigated as an anticonvulsant. However, in certain of the earlier studies improvement in behavioural patterns was noted. Haran (1) reported that sulthiame reduced irritability and violent behaviour and improved the sociability of epileptic patients, and Ingram and Radcliffe (2) found that hyperkinetic behaviour of 16 out of 18 patients in their study was either 'abolished or improved'. Liu (3) noted an overall improvement in the behaviour of 32 out of 50 patients. In 12 of 18 hyperkinetic children, Kneebone (4) stated that there had been 'significantly improved behaviour'. Two double blind trials (5, 6) have confirmed that sulthiame is significantly effective in reducing the incidence of disturbed behaviour in mentally handicapped patients.

Yarden (7) claimed that a combination of sulthiame and trifluperazine reduced the incidence of psychotic outbursts in 24 chronic schizophrenics, and in view of these findings he decided to examine the possible benefit of sulthiame in patients in an adult psychiatric hospital setting who presented with disturbed behaviour as a symptom of either functional or organic psychiatric illness. Accordingly 30 patients at Leverndale Hospital, Glasgow, manifesting disorganized hyperactivity, general restlessness and inappropriate aggression, regardless of diagnosis, were started on sulthiame, administered in a dose of up to 250 mg three times daily in conjunction with the previous medication.

Continued administration of sulthiame to 13 schizophrenic patients for periods from 6 to 12 months resulted in no improvement. Two hypomanic patients were given sulthiame in addition to phenothiazines without improvement; and of 4 patients, a confused geriatric and 3 non-geriatric brain-damaged adults, 3 failed to show any benefit from the sulthiame medication.

However, the abnormal behaviour of patients with epilepsy appeared to respond, with improvement in 12 of 17 patients. There was diminution in hostility and destructive attitudes. Patients were quietened, and management became less of a problem. Fit frequency did not alter.

Sulthiame was introduced to the patients' drug