3. Interactions between psychotherapy and other treatments having a different theoretical and empirical basis, including the use of drugs and social measures.

Applications are likely to be more favourably received if they refer not to ill-defined conditions like 'personality disorder' but to groups of patients diagnosed as suffering from a neurotic disorder with identifiable or definable symptoms or associated conditions such as attempted suicide, phobias, situational crises like bereavement, or reactions to chronic medical or psychological disabilities. The methods of treatment proposed for study should, as far as possible, be described in specific terms.

Applicants may ask for whatever is needed to carry out the study to evaluate methods of treatment, though it should be noted that salary support for psychotherapists actually carrying out the treatments would need careful scientific justification and that no administrative overheads can be provided.

A. J. BULLER
Chairman MRC Neurosciences Board
D. A. POND
Chairman MRC Subcommittee on Psychotherapy
Medical Research Council, 20 Park Crescent, W1N 4AL

FAMILY AND SOCIAL FACTORS AND THE COURSE OF SCHIZOPHRENIA

DEAR SIR,

The studies of Brown, Birley and Wing on the influence of family relationships on outcome in schizophrenia, reported in their replication study (*Journal*, September 1972, 121, p 241) and replicated again by Vaughn and Leff (*Journal*, August 1976, 129, p 125), are gaining general acceptance in the United Kingdom and therefore require to be carefully assessed in the light of other work done in this field. Their studies, showing that high Expressed Emotion (EE) by a key relative towards the patient, independently of other events, predicts relapse have two main points of weakness. These arise from the composition of the samples. The sample used in the 1972 paper is composed of 27 per cent first admissions, the remainder of the patients being divided about equally between those with a history of less than five years, and those with a history of more than five years, since first breakdown. The pattern of outcome in schizophrenia is usually quite apparent by two years and often by one year after first breakdown. Thus Brown and his co-workers are, in the majority of cases, rating EE in key relatives and using this as the key predictor of relapse when the pattern of outcome is already known. For instance, in the table showing correlations between the variables, previous admissions are significantly related to relapse and rank only second to high EE (p 258, 1972 paper).

Secondly, in using readmissions these workers are depriving themselves of direct access to the question of how high EE arises and when. For this purpose they have to use inferences derived from partial correlation coefficients and retrospective ratings. These weaknesses could be avoided by using a sample of first admission patients. The Napsbury Family Research Unit has recently completed a four year study of 40 first admission schizophrenics from parental homes. Using a self-rating interpersonal perception technique (1970), patient and parents were tested shortly after the first admission and again 2½ years later. In this study, Brown's concepts were not used, but the test scoring available from this study is easily adapted to score a number of critical comments made by parents about the patient, as well as to provide some measure of degree of parental involvement with the patient (two central features of EE). We therefore scored the test material in this way and found that the test given soon after first admission had some power to predict good and poor outcomes 2½ years later, these being rated in terms of a patient's capacity to function socially and at work. It also gave some distinction between those who relapsed and those who did not during the nine months after first admission ($P < \cdot 04$ Mann Whitney). The second test given at follow-up showed that the association between the test score and these two measures of outcome had increased enormously ($P < \cdot 0002$).

If we accept the thesis that high EE as an independent factor is a cause of relapse, and that the test scoring indicated above provides some measure of EE, then our findings may be summarised as: (a) high EE is likely to have been present in 20–30 per cent of parents long before the first breakdown and to have been a factor leading to it; (b) in patients with good outcomes, the test score thought to be associated with EE decreases dramatically during the follow-up period; (c) in patients with poor outcomes, high EE develops very early on (probably quite abruptly) and thenceforth shows no significant change; it becomes encapsulated, thus rendering the parents' attitude unrelated to other events, including how well or ill the patient is; this in turn causes relapse and maintains the illness; and (d) whether (b) or (c) occurs is, in about 75 per cent of cases, closely related to the patient's attitudes to his parents (1975).

R. D. SCOTT
T. FAREWELL
D. PARIENTE
Napsbury Family Research Unit, Napsbury Hospital,
Nr St Albans, Herts

References

Scott, R. D., Ashworth, P. L. & Casson, P. D. (1970) Violation of parental role structure and outcome in schizophrenia: a scored analysis of features in the patient-parent relationship. *Social Science and Medicine*, 4, 41–4.

Scott, R. D. (1975) Family patterns and outcome in schizophrenia. In *New Perspectives in Schizophrenia* (eds A. Forrest, and J. Affleck), pp 156–88 Edinburgh: Churchill-Livingstone.

PROLONGED PARKINSONIAN REACTION AFTER HALOPERIDOL IN A PATIENT WITH MONOCLONAL IgM

Dear Sir,

The binding of drugs to plasma proteins is an important determinant of drug concentration and therapeutic efficacy (Dayton *et al*, 1973). Studies thus far have pertained to patients with normal concentrations of plasma proteins and the albuminopathies (Koch-Weser and Sellers, 1976). The pharmacokinetic significance of clinical entities involving elevations of paraproteins (i.e. monoclonal immunoglobulins), e.g. multiple myeloma, Waldenström's macroglobulinemia, benign monoclonal gammopathy (BMG) has not hitherto been studied. These paraproteins, in contrast to polyclonal immunoglobulins found in normals, are homogeneous in structure and function. They possess antibody and non-immunologic binding properties (Farhangi and Osserman, 1976; Seligmann and Brouet, 1973; Thomas *et al*, 1974). A drug-binding capacity for paraproteins would enhance drug storage and prolong pharmacologic effect.

An 82-year-old woman was admitted to the psychiatric unit for treatment of a senile psychosis characterized by behavioural and sensorial changes, delusions, and auditory hallucinations. Treatment was initiated with haloperidol, starting at 1 mg/per day with gradual increase to 9 mg chlorpromazine 50 mg was given at bedtime. A moderately positive response permitted her discharge from the hospital, reduction of haloperidol to 3 mg per day, and discontinuation of chlorpromazine. About four weeks later, she developed a severe Parkinsonian reaction manifested by hypokinesis, bradykinesis, rigidity, and sialorrhea. The haloperidol was then discontinued, but the reaction persisted for 12–14 days thereafter. A remarkable symptomatic improvement of several weeks' duration was noted after its clearance.

Blood drawn one day after initiation revealed a sedimentation rate of 104 mm/hr (normal 0–15) and an alkaline phosphatase of 110 mu/ml (normal 30–85). Diagnostic studies revealed no evidence of malignancy. Serum viscosity was 1·97 (normal 1·4–1·7). Immunoelectrophoresis revealed abnormal values for IgM. The first study, done 20 days after initiation of haloperidol, revealed an IgM level of 4200 mg percent (normal 100); second and third determinations, done at 22 and 34 days, showed IgM levels of 4200 and 2800 mg per cent respectively. The levels of IgG and IgA were within normal range. Bone marrow aspirations were negative for myeloma and a diagnosis of BMG was made. In all probability these abnormalities pre-dated treatment with haloperidol, but the remote possibility of drug antigenicity was considered. Pre-treatment studies were not performed.

Data suggestive of an hypothesis of paraprotein binding are the binding affinity of haloperidol (92 per cent), its serum half-life of 12–22 hours, and the half-life of IgM being 6–7 days with 75 per cent metabolism in 12–14 days. Discontinuation of haloperidol usually results in prompt subsidence or brief duration of dyskinesias but persistent Parkinsonism of 12–14 days is not common.

In order to ascertain if the monoclonal IgM had any haloperidol-binding property 25 ng of tritiated haloperidol (a gift from McNeil Laboratories, Inc, Fort Washington, Pa) was incubated for 1 hour with 0·1 ml of serum of patient and normal control respectively. Ouchterlony (double gel diffusion) analysis in 1 per cent agar was performed with anti-IgM. Radioactivity of the precipitin line was determined by autoradiography over a period of 14 days. No evidence of binding of haloperidol to IgM was found in either patient or normal control serum.

E. Rice

Dept of Psychiatry, Mount Sinai School of Medicine, City University of New York, Fifth Avenue and 100th Street, New York, New York 10029

References

Dayton, P. G., Israili, Z. H., & Perel, J. M. (1973) Influence of binding on drug metabolism and distribution. *Annals of the New York Academy of Science*, 226, 172–94.

Koch-Weser, J. & Sellers, E. M. (1976) Binding of drugs to serum albumin. *New England Journal of Medicine*, 294, 311–16.

Farhangi, M. & Osserman, E. F. (1976) Myeloma with xanthaderma due to an IgG monoclonal anti-flavin antibody. *New England Journal of Medicine*, 294, 177–83.

Seligmann, M. & Brouet, J. C. (1973) Antibody activity of human myeloma globulins. *Seminars In Hematology*, 10, 163–77.

Thomas, D. W., Rosen, S. W., Kahn, C. R., Temple, R., & Papadopoulos, N. M. (1974). Molecular lactic acid dehydrogenase: a cause of increased serum lactic dehydrogenase activity. *Annals of Internal Medicine*, 81, 434–9.