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Response to drugs in schizophrenia: the influence of family history, obstetric complications and ventricular enlargement

V. L. NIMGAONKAR,[1] S. WESSELY, L. E. TUNE AND R. M. MURRAY
From the Institute of Psychiatry, London and Phipps Clinic, Johns Hopkins Medical School, Baltimore, USA

SYNOPSIS A prospective study of antipsychotic drug treatment showed no difference in response between schizophrenic in-patients with or without a familial predisposition to the illness ($N = 53$). All patients received at least 600 mg chlorpromazine equivalents antipsychotic medication for 6 weeks. Ventricle brain ratios, ratings of cortical sulcal widening and a history of obstetric complications also failed to account for the variability, but early age of onset was associated with unsatisfactory response.

INTRODUCTION

The clinical efficacy of chlorpromazine and related drugs in the treatment of the clinical features of schizophrenia is well established (Cole *et al.* 1966; Goldberg *et al.* 1965). However, a significant number of patients fail to respond to medication (Kolakowska *et al.* 1985). The prospective identification of such patients would be an important advance, permitting more rational use of antipsychotic drugs.

The response to drug treatment in schizophrenia may be influenced by clinical features of the psychosis, pharmacological factors, and factors related to the aetiology of the illness. Most workers agree that diagnostic subtypes of schizophrenia do not account for the variability of response (Hirsch, 1986). There is a further consensus that the so-called 'positive' symptoms of schizophrenia, such as hallucinations and delusions, respond better to neuroleptics than 'negative' symptoms, such as flattened affect and apathy (Csernansky *et al.* 1985). There is less agreement about the relevance of paranoid symptoms, which have been associated with either a better (Goldberg *et al.* 1965) or a worse response (Hollister, 1974). Conflicting evidence also exists concerning the relationship between pre-morbid adjustment and treatment response. Impaired pre-morbid social functioning was associated with poor response to phenothiazines by Klein & Rosen (1973), and with good response to phenothiazines by Goldstein (1970) while Hollister (1974) found no relationship.

Considerable interest was focused initially on the possible specificity of different neuroleptic drugs for individual psychotic symptoms (Hollister *et al.* 1974), but such a specificity has remained elusive. Clinical judgement remains the best guide to the nature and dosage of medication (Hirsch, 1986). A past history of satisfactory neuroleptic response is a good predictor of response on subsequent occasions (Kolakowska *et al.* 1985). The complex metabolism of antipsychotic drugs makes it difficult to analyse the influence of pharmacokinetic factors (Curry, 1986), but these do not appear to account for failure of treatment, provided poor compliance and inadequate dosage are taken into account (Smith *et al.* 1979; Gelder & Kolakowska, 1979; Kolakowska *et al.* 1980).

Both heredity (Gottesman & Shields, 1982) and brain damage (Davison & Bagley, 1969) have been implicated in the aetiology of schizophrenia. It is possible that these factors may operate through different pathogenic mechanisms in the brain. Consequently, differential clinical response to pharmacotherapy has not been investigated satisfactorily.

It has recently been suggested that cases of

[1] Address for correspondence: Dr V. L. Nimgaonkar, Western Psychiatric Institute and Clinic, 3811 O'Hara Street, Pittsburgh, USA 15217.

schizophrenia be divided for research purposes into those with a family history of major psychiatric illness ('familial') and those without such a history ('sporadic' or 'non-familial') (Murray *et al.* 1985). The proponents of this approach have stated: 'genetic variables are more important in familial schizophrenia and environmental variables are more important in sporadic schizophrenia' (Kendler & Hays, 1982). This dichotomy would be strengthened if there was a greater prevalence of alternative aetiological indicators, such as brain damage, among the 'non-familial' cases. Earlier work (McNeil & Kaij, 1978; Lewis & Murray, 1987) suggested that a history of obstetric complications is more frequent among schizophrenic patients than among non-psychotic controls. Owen *et al.* (1988) have recently reported that a history of obstetric complications is more likely to be recorded when a family history is absent. Moreover, perinatal trauma is associated with both periventricular haemorrhage in children, and evidence of residual brain damage in the form of ventricular dilatation (Lancet, 1985). CT scan data from schizophrenic patients also suggests a greater likelihood of brain damage among non-familial cases. Of the nine studies to date, Lewis *et al.* (1987) reported that five have shown a negative association between ventricular enlargement and the presence of a family history, three have shown no relationship, and one has shown a positive association. There is also a greater likelihood of cortical atrophy among non-familial cases (Oxenstierna *et al.* 1984).

The higher prevalence of brain damage in the 'non-familial' group may have implications for drug therapy. Kleinman and his colleagues (1982, 1984) suggest that changes in prolactin response and eye blink rates following neuroleptic challenge reflect drug-induced blockade of brain dopaminergic receptors, and claim that these changes are reduced in schizophrenic patients with ventricular enlargement. This suggests that reduced brain dopamine (DA) function may occur in association with evidence of brain damage. Since the clinical effects of antipsychotic drugs appear to be related to DA blockade in the brain (Johnstone *et al.* 1978), one can postulate that ventricular enlargement predicts unsatisfactory clinical response.

Weinberger and his colleagues (1980) suggested an association between increased ventricular brain ratio (VBR) and unsatisfactory response to neuroleptics. Six further studies have been published (Table 1). Two agree with the initial finding (Schulz *et al.* 1983; Luchins *et al.* 1984), while two find no relationship (Nasrallah *et al.* 1983; Williams *et al.* 1985). However, the two most recent studies, which are prospective in design, draw different conclusions. Losonczy and his associates (1986) report a trend for improved response to neuroleptics with increased VBR, but even with generous criteria for response, only seven such patients were identified. Smith *et al.* (1985) added further refinements by comparing per cent changes in symptom scores with VBR, rather than using arbitrary cut-offs for response or ventricular enlargement. Furthermore, by using minimum

Table 1. *Relationship between VBR and clinical response to neuroleptic drugs*

Study	Design	No. of patients	Specification of Treatment: Minimum dose	Specification of Treatment: Minimum duration (weeks)	Assessment of response	Relationship between VBR and clinical response
Weinberger *et al.* (1980)	Retrospective	20	+	8	BPRS	Inverse relationship
Nasrallah *et al.* (1983)	Retrospective	55	–	–	Clinical judgement	Not detected
Schulz *et al.* (1983)	Retrospective	12	–	Mean 3·5	Total scores on BPRS	Trend for inverse relationship
Luchins *et al.* (1984)	Retrospective	35	+	5	GAS/SADS-C	Inverse relationship
Williams *et al.* (1985)	Retrospective	40	–	4	Clinical judgement	Not detected
Smith *et al.* (1985)	Prospective	39	+	3	BPRS	Trend for positive correlation with psychosis factor scores
Losonczy *et al.* (1986)	Prospective	19	+	6	BPRS/CGI	Not detected

BPRS = Brief Psychiatric Rating Scale; GAS = Global Assessment Scale; SADS-C = Schedule for Affective Disorders (change); CGI = Clinical Global Inventory.

treatment schedules and measuring plasma drug concentrations, they were able to analyse separately 32 patients who had serum neuroleptics levels within an arbitrary therapeutic range. The results show a weak positive correlation between VBR and improvements in positive symptoms. Although these results did not reach conventional levels of statistical significance and the treatment period of three weeks may not have been sufficient to assess neuroleptic response adequately, the findings contradict the earlier reports.

In view of the suggested difference in structural brain damage between 'familial' and 'non-familial' groups and its implications for DA function in the brain, it can be postulated that the two groups differ in the clinical response to antipsychotic drugs. An earlier retrospective study suggests that patients with a history of maternal psychiatric illness respond better than those without such a history (Cole *et al.* 1966). The present study was designed to investigate the possibility of differences in clinical response between 'more-genetic' and 'less-genetic' forms of the illness.

Specifically, the role of familiality, obstetric complications and brain damage in pharmacological response was assessed. It was predicted that patients with a family history of psychotic illness would respond better to drugs than those lacking such a history, while a history of obstetric complications or ventricular enlargement would be associated with a less satisfactory response.

METHODS

Clinical assessments

Consecutive admissions to the Maudsley Hospital between October 1985 and July 1986 were screened. Consenting in-patients who met the Research Diagnostic Criteria (RDC) of Spitzer *et al.* (1977) for schizophrenia were assessed within 24 hours of admission, using both the Global Assessment Scale (Endicott *et al.* 1976) and the Schizophrenia Scale of Montgomery *et al.* (1983) (MSS). The MSS consists of items covering both non-psychotic and psychotic phenomena; each item is rated on a 0–6 scale (0 = absent, 6 = maximal severity). Symptom severity was also assessed after six weeks of therapy using the MSS by an observer blind to the initial ratings and to family history, obstetric history or VBR. The scores on the MSS were summated to provide a total symptom score (TSS). The inter-rater reliability for measurement of TSS was satisfactory. (Intraclass coefficient = 0·95, $N = 9$. Bartko & Carpenter, 1976).

Demographic and clinical information was obtained from the patients' notes and by administering the Schedule for Affective Disorders and Schizophrenia (Spitzer & Endicott, 1978). Lifetime neuroleptic dose was calculated and converted to chlorpromazine equivalent units using standard conversion factors (Davis, 1976). Psychiatric information about first and second degree relatives was gathered by interviewing at least one relative, using a structured questionnaire (Reveley, unpublished). Hospital discharge summaries for relatives were obtained where appropriate. Diagnosis of psychiatrically ill relatives by Family History RDC (Endicott *et al.* 1975) was undertaken by an observer (R.M.M.) blind to all clinical details about the probands. The following diagnostic categories were used: schizophrenia, affective psychosis, schizoaffective psychosis, atypical psychosis and other mental illness. Patients with a first or second degree relative diagnosed to have psychosis were classed 'familial', while those without such a history were considered 'non-familial'. Details of obstetric complications were also obtained from a relative by administering the questionnaire of Lewis & Murray (1987). Patients were rated on a three point scale by a rater (R.M.M.), blind to the family history and clinical details of probands, as follows: 0 = no obstetric complications, 1 = equivocal, 2 = definite. Further details of the familial, obstetric and CT scan ratings can be found in Lewis *et al.* (1987).

CT Scans

Brain CT scans were performed using a model 1010 CT scanner. Lateral ventricle to brain ratios were measured by manual planimetry at the slice showing maximal ventricular dilatation. The size of the lateral ventricles and of the intracranial space, was measured, and VBR calculated by the method of Synek & Reuben (1976). Planimetry was performed by an observer blind to the clinical details of the patients. VBRs were measured at least thrice in each case, and the two identical values used for analysis. The

test–retest reliability for measurement of VBR was satisfactory (Pearson's product moment correlations; $r = 0{\cdot}80$, $P < 0{\cdot}02$; $N = 20$), and the inter-rater reliability was significant at the $P < 0{\cdot}05$ level in comparison with an independent rater ($r = 0{\cdot}78$; $N = 19$). The results presented here were measured by one of the authors (V. N.). Sulcal widening was rated blind by the same observer, using the method described by Owen *et al.* (1988). Further details are available in Nimgaonkar *et al.* (1988).

Drug Treatment

A dosage of 600 mg chlorpromazine equivalent units/day for six weeks was specified as the minimum for the study. Patients who received less than 600 mg chlorpromazine equivalent units/day for the duration of the study were not included in the analysis. Drug dosage was determined by the clinician in charge of the patient. The following antipsychotic drugs were used: chlorpromazine, haloperidol, trifluoperazine, thioridazine, sulpiride, pimozide, flupenthixol and fluphenazine. Anticholinergic medication (procyclidine or orphenadrine) was prescribed as necessary, and was monitored. At the time of the final clinical assessment, DA blocking activity in serum was measured using a radioreceptor assay (Tune & Coyle, 1982) and was used as a measure of serum neuroleptic concentrations.

RESULTS

The reasons for admission were as follows: first admission for acute psychosis with behavioural disturbance ($N = 13$), acute psychotic relapse with behavioural disturbance ($N = 28$), acute psychotic relapse with little behavioural disturbance ($N = 4$), chronic psychosis with florid features and severe behavioural disturbance ($N = 4$), chronic psychosis with mainly negative features ($N = 2$), chronic psychosis referred for investigations ($N = 2$). 53 patients completed the study. The following patients were excluded: four were discharged before an initial screening could be completed; one declined to participate initially and three others subsequently. Three cases who completed the period of the study were subsequently excluded due to inadequate medication. Data from these patients were not used for analysis. A full family history could not be obtained in two cases and obstetric information was unavailable for four patients. Eight patients declined to have a CT scan. Information about family histories and obstetric complications was obtained from the following sources: mothers (35 cases), other first degree relatives (13 cases) or second degree relatives (6 cases). Psychiatric details about 242 first degree relatives and 535 second degree relatives were obtained.

Clinical details of 'familial' and 'non-familial' cases are given in Table 2. There were 22 patients in the familial group and 29 patients in the non-familial group. The two groups did not differ with respect to age, sex, race, weight, duration of illness, lifetime neuroleptic medi-

Table 2. *Demographic and clinical details of patients*

	'Familial' ($N = 22$)	'Non-familial' ($N = 29$)
Age	32·4 ± 2·4	32·3 ± 2·0
Male: Female ratio	15:7	20:9
Race (Caucasian/Afro-Caribbean/Other)	10:9:3	19:10:0
Weight (kg)	70·3 ± 2·0	72·1 ± 2·3
Duration of illness (months)	92·3 ± 14·6	84·6 ± 13·8
Lifetime neuroleptic intake (G chlorpromazine units)	340·9 ± 78·1	490·0 ± 188·5
Duration of present episode (weeks)	34·9 ± 10·8	80·7 ± 28·0
Number of admissions	2·9 ± 0·6	2·9 ± 0·5
Global Assessment score at start of treatment	48·9 ± 5·1	45·3 ± 4·3

Values are shown as mean ± S.E. mean. Variables were compared using the Mann-Whitney *U* test or the Chi-squared test (for sex and race).

Table 3. *Details of pharmacological treatment*

Pharmacological treatment	'Familial' ($N = 22$)	'Non-familial' ($N = 29$)
Oral medication (mg chlorpromazine units/day)	1635·1 ± 432·8	1639·3 ± 417·2
Parenteral medication (mg chlorpromazine units/day)	372·4 ± 103·6	503·1 ± 193·1
Total medication (mg chlorpromazine units/kg/day)	28·3 ± 6·2	28·3 ± 5·4
Serum dopaminergic blocking activity (ng chlorpromazine units/ml)	125·0 ± 42·0	135·2 ± 40·7
Number of patients on anticholinergic medication	9	19

Values are shown as mean ± S.E. mean in each group. Comparisons between the two groups were made by the Mann-Whitney *U* test or the Chi-squared test as appropriate.

cation, duration of present episode or number of admissions. There was no difference between the two groups with respect to the number of patients who had received electroconvulsive treatment or lithium in the past. The two groups also did not differ in the dosage of oral or parenteral medication received in the study period or with respect to mean DA blocking activity in the serum (Table 3). Similar numbers of patients in each group received anticholinergic medication.

Response to medication

Neither the total symptom scores nor Global Assessment Scores (Table 2) differed significantly between the two groups at the beginning of the study. Similarly, there was no difference in scores for individual symptoms in the MSS. In both groups a significant reduction in total symptom scores was noted following therapy ($P < 0{\cdot}005$, paired Student's t test) (Fig. 1).

The relationship between familiality and clinical response was examined by analysis of variance, and also by dichotomizing the patients on the basis of response.

Analysis of variance

The TSS for the cohort at the beginning of the study were normally distributed, but were skewed to the left at the end of the study. A measure of change following log transformation of TSS was therefore used for analysis. The value (log Y − log X) was calculated for each patient, where X = TSS at the beginning of the study and Y = TSS at the end of the study. An analysis of variance using presence or absence of family history as the independent variable and the value (log Y − log X) as the dependent variable failed to show a significant difference ($F = 0{\cdot}02$). The following factors were next used as covariates: age, duration of illness, lifetime antipsychotic dose, duration of treatment for illness, duration of present episode, and duration of treatment for the present episode prior to admission. Familiality again failed to account for the variance noted, but age and duration of present episode as well as duration of treatment for the present episode before admission significantly influenced response (Table 4). Similar results were obtained if 'familiality' was based on the following criteria: presence of a first degree relative with schizophrenia, presence of a first degree relative with any psychosis, or the presence of a first or second degree relative with schizophrenia (RDC).

In view of the significant influence of age, duration of the present episode and duration of prior treatment for the present episode on clinical response, the relationship between each of these three variables and the value (log Y − log X) was examined. A significant positive correlation between age and symptom change was obtained (Pearson's product moment correlation, $r = 0{\cdot}42$, $P < 0{\cdot}001$, two tailed test). The negative

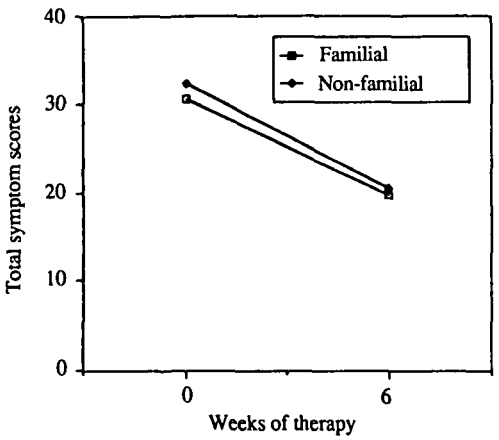

FIG. 1. Change in total symptom scores with treatment. The bars represent S.E. means. * $P < 0{\cdot}005$ different from initial score in each group, paired Student's t test.

Table 4. *Effect of familiality on change in total symptom scores (Analysis of variance)*

Source of variation	Sum of squares	df	F Ratio
Family history of psychosis	0·03	1	0·13
Covariates	6·82	6	4·69
Duration of present episode (weeks)	1·78	1	7·34**
Duration of treatment for present episode (days)	1·05	1	4·34*
Duration of illness (months)	0·22	1	0·93
Lifetime neuroleptic dose (G chlorpromazine units)	0·43	1	1·79
Duration of treatment for illness (weeks)	0·77	1	3·19
Age	3·40	1	14·03**
Explained	6·85	7	4·04**
Residual	10·91	45	—
Total	17·76	52	—

Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS-X, 1983).

* $P < 0{\cdot}05$; ** $P < 0{\cdot}005$.

correlation between duration of the present episode and symptom change just failed to reach conventional levels of statistical significance ($r = 0{\cdot}24$, $P = 0{\cdot}07$), and no significant correlation between duration of prior treatment and clinical response was noted ($r = 0{\cdot}02$, $P = 0{\cdot}15$).

Dichotomization of response

The percentage change in TSS during the study was calculated for each case and the frequency distribution plotted (Fig. 2). The distribution was skewed towards responsiveness. The cohort was divided arbitrarily into those who showed more than 80% improvement in total symptom scores ('responders') and those who showed less than 20% improvement ('non-responders'). The two groups were compared with respect to demographic, clinical and pharmacological variables (Table 5). The non-responders were significantly younger than the responders, and were less likely to have cohabited with a sexual partner. In addition, the non-responders had an earlier age of onset of the illness, but no significant differences in duration of illness or lifetime neuroleptic dose were observed. There were no significant differences in the racial or sexual composition of the two groups. As expected, the non-responders received a higher dose of antipsychotic medication during the study period. Though the non-responders had a higher mean DA blocking activity in the serum than the responders, this difference failed to reach statistical significance. The prevalence of cases with a positive family history was similar among the two groups.

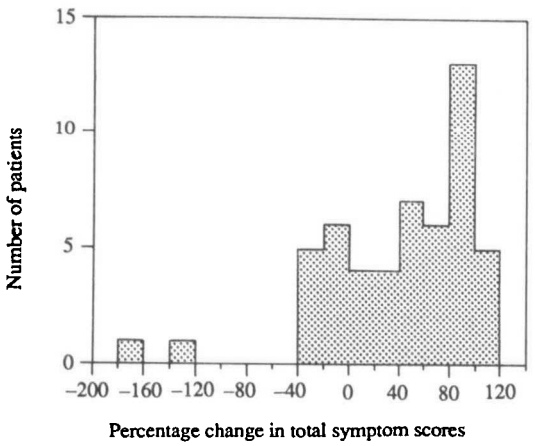

FIG. 2. The percentage change in Total Symptoms Scores (TSS) was calculated from the TSS at the beginning and end of the study in each case. A negative value indicates worsening in symptoms, while a positive value signifies improvement.

An analysis of the power of the present techniques to measure differences in response between the familial and non-familial groups was also performed (Pocock, 1983). The size of a 1·45 fold difference in log transformed change in TSS between the sample used would enable identification of the two groups, significant at

Table 5. *Characteristics of responders and non-responders*

	Responders ($N = 18$)	Non-responders ($N = 18$)
Age	36·5 ± 3·0	27·4 ± 1·1*
Sex (male/female)	9/9	13/5
Marital status (single/cohabiting/separated)	10/4/4	17/0/1*
Race (Caucasian/Afro-Caribbean/Other)	9/7/2	9/9/0
Age of onset of illness	25·9 ± 2·0	20·0 ± 0·7**
Duration of illness (months)	94·4 ± 19·0	68·8 ± 9·8
Antipsychotic medication (mg chlorpromazine units/kg/day)	16·3 ± 4·0	43·6 ± 8·3***
Lifetime neuroleptic dose (G. chlorpromazine units)	323·3 ± 132·3	524·2 ± 277·1
Serum dopaminergic blocking activity (ng chlorpromazine units/ml)	92·2 ± 41·0	184·3 ± 59·6
History of psychosis in first degree relative	9†	8
History of definite obstetric complications	2†	5
VBR	10·2 ± 0·4 ($N = 15$)	9·7 ± 0·6 ($N = 15$)
Number on anticholinergic medication	8	10

'Responders' are patients who showed more than 80% improvement in total symptom scores. 'Non-responders' showed less than 20% improvement. Values are mean ± S.E. mean. Comparisons were made using the Mann–Whitney U test or the Chi squared test as appropriate.

* $P < 0{\cdot}05$; ** $P < 0{\cdot}01$; *** $P < 0{\cdot}0005$.

† Data not available for one case in this group.

Table 6. *Power analysis*

Minimum detectable change in group means $\frac{(\mu_1-\mu_2)}{\mu_2}$	Standardized difference $\frac{(\mu_1-\mu_2)}{\sigma}$	Number required in each group (N)
2·29	1·61	10
1·45	1·02	25
0·73	0·51	100
0·32	0·23	500
0·23	0·16	1000

The minimum number of patients (N) required in each group to detect a difference in group means (μ_1 and μ_2) significant at the $P < 0{\cdot}05$ level was calculated from the following formula:

$$N = \frac{(\mu_2)^2}{(\mu_2-\mu_1)^2} f(\alpha, \beta)$$

α (the risk of a false positive result) and β (the risk of a false negative result) were both set at 0·05. In the present analysis, μ_1 (mean change in log transformed values for TSS after treatment in the non-familial group) and μ_2 (mean change in log tranformed values for TSS after treatment in the familial group) were 0·41 and 0·50 respectively, and σ (the standard deviation of μ_1) was 0·58. Values for $f(\alpha, \beta)$ were obtained from Geigy (1970).

Table 7. *Analysis of variance: influence of obstetric complications on response to drugs*

Source of variation	Sum of square	df	F ratio
Obstetric complications	0·21	1	0·71
Covariates	4·74	6	2·72*
Age	3·16	1	10·88**
Duration of illness (months)	0·11	1	0·39
Duration of present episode (days)	0·24	1	0 81
Duration of treatment for illness (weeks)	0·30	1	1·03
Lifetime neuroleptic dose (G chlorpromazine units)	0·65	1	2·24
Duration of prior treatment for present episode (days)	0·21	1	0·74
Explained	4·94	7	2·44*
Residual	7·83	27	—
Total	12·78	34	—

Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS-X, 1983).
* P 0·06; ** P 0·005.

the $P < 0{\cdot}05$ level. Estimated changes in sensitivity using large numbers of patients are displayed in Table 6. Approximately 950 patients in each group would be required to attain statistical significance ($P < 0{\cdot}05$), given the differences in mean value for change in total TSS in the familial and non-familial groups found in the present study.

Influence of obstetric complications on response

Eleven cases with a definite history of obstetric complications were identified. Twenty-five others had normal obstetric histories, while obstetric details for the rest were unavailable or equivocal. Comparisons were made between patients with or without a definite history of obstetric complications. A history of definite obstetric complications failed to account significantly for the log transformed change in TSS following treatment (log Y − log X), even when the following covariates were employed: age, duration of illness, duration of present episode, duration of treatment for the illness, lifetime neuroleptic dose and the duration of treatment for the present episode prior to admission (Table 7). However, age did account significantly for the variance, while the variation due to dose of antipsychotic medication prescribed during the study just failed to reach statistical significance. Though a history of obstetric complications was more likely to occur among non-responders than among responders, the difference did not reach statistical significance (Table 5).

Relationship between CT scan measures and response

There was no significant correlation between VBR and the log transformed change in TSS following therapy (log y − log X) (Pearson's product moment correlation, $r = -0{\cdot}09$, $N = 45$). A statistically significant difference in mean VBR between responders and non-responders was not observed (Table 5). There was no significant correlation between the total score for sulcal widening and log transformed change in TSS ($r = 0{\cdot}11$, $N = 45$). Dichotomization on the basis of absence or presence of any sulcal widening did not yield significant differences in response ($F = 0{\cdot}01$, $N = 45$).

DISCUSSION

In this study, bias was reduced by employing a prospective design and by examining consecutive admissions. The MSS not only provides a reasonably accurate estimate of the clinical state, but also consists of items shown to correlate favourably with global improvement following pharmacotherapy (Montgomery *et al.* 1983). Observer bias was reduced by employing two

'blind' raters with good inter-rater reliability. Patients were assessed on admission, at a time when symptoms were most severe. Compliance was ensured by use of an in-patient sample.

As there is no evidence that neuroleptics differ in their antipsychotic properties (Hollister *et al.* 1974), choice of drug and dosage was left to the clinician. Administration of anticholinergic drugs can reduce the clinical efficacy of antipsychotic drugs (Lader, 1979), but the numbers of patients prescribed such drugs did not differ between the groups. Patients in the various groups under comparison received similar doses of antipsychotic medication. The serum dopaminergic blocking activity, which was used to estimate concentrations of drugs and their active metabolites, was also similar. Though a significant correlation between oral dose and serum dopaminergic blocking activity has been obtained for several antipsychotic drugs, there are notable exceptions such as thioridazine and trifluoperazine (Krska *et al.* 1986). Therefore, this parameter was not used as a covariate in the analysis of variance. An arbitrary minimum dose of antipsychotic medication was required for inclusion in the study. Only three patients were excluded for this reason, and their inclusion would not have altered non-significant differences between the groups compared.

In spite of differences in methodology, our study is in agreement with previous reports on treatment and outcome in schizophrenia. We found that duration of the antipsychotic episode prior to admission was inversely related in clinical response though this failed to reach levels of statistical significance. This may suggest that early commencement of pharmacotherapy increases an individual's likelihood of clinical improvement. Both Crow *et al.* (1986) and May *et al.* (1981) found that early treatment decreased the likelihood of relapse. Younger patients were less likely to respond satsifactorily to medication (Table 4), in agreement with the findings of Cole *et al.* (1966). These findings may be related to earlier onset of the illness in such individuals, and suggest that an early onset heralds a drug resistant form of the illness. Alternatively, the findings could be used in support of the suggested association between asociality and unsatisfactory response (Klein & Rosen, 1973). Indeed, the non-responders were less likely to have cohabited with a sexual partner than the responders.

A familial versus non-familial dichotomy based on the presence or absence of psychosis in a first or second degree relative was intended to differentiate between patients with or without genetic predisposition. Eaves *et al.* (1986) have criticized such a strategy on the grounds that both 'false positives' and 'false negatives' can occur with sufficient frequency to blur any potential differences. Since the non-familial group is likely to include some individuals with a genetic predisposition, it may be that a full examination of whether cases of schizophrenia with a genetic predisposition differ in drug response from those without a predisposition will have to await the discovery of a genetic marker of that vulnerability. However, such a strategy has yielded differences in clinical profiles (Shur, 1982), prognostic factors (Baron *et al.* 1982), presence of structural brain abnormalities (Reveley *et al.* 1984) and a history of obstetric complications (Owen *et al.* 1988).

In the present study, a pharmacogenetic approach (Murray & Murphy, 1978; Galdi *et al.* 1981) was used to investigate differences in schizophrenic patients. Such an approach can yield valuable clues about the functional pathology mediating disease processes. We were unable to detect differences in response to antipsychotic drugs between schizophrenic patients with or without a family history of psychosis. These findings, together with the absence of significant differences in clinical features (Baron *et al.* 1982) between the 'familial' and 'non-familial' patients, suggest that the alterations in neuronal function mediating the disease process are similar in the two groups in spite of possible differences in aetiology. In addition, the failure to find differences in mean VBR suggests no difference in the amount of coarse brain damage between our familial and non-familial groups.

It is unlikely that the failure to find a significant difference in response between the familial and non-familial groups can be attributed to the size of the study. The difference in mean values for change in total symptom scores between the two groups would require approximately 1900 patients to attain conventional levels of statistical significance. In comparison,

Johnstone *et al.* (1978) were able to demonstrate a drug-placebo difference in a study involving only 45 patients. The difference, if any, noted here between the two groups is therefore unlikely to be of clinical significance.

The use of the RDC meant that schizoaffective patients were not represented in the cohort. Such patients have a better outcome than schizophrenic patients (Brockington *et al.* 1980*a*, *b*), and it is also possible that 'familial' cases are more likely to have affective features (Shur, 1982). The exclusion of schizoaffective psychosis may consequently have biased the sample against familial cases likely to show a favourable response to antipsychotic drugs.

The putative relationship between VBR and response to antipsychotic drugs (Weinberger *et al.* 1980) is appealing, because it suggests that destruction of neural tissue is associated with altered brain function. However, we were unable to find a significant correlation between response to neuroleptics and ventricular enlargement, nor was a difference in mean VBR between 'responders' and 'non-responders' detected. In addition, a history of obstetric complications, which has been suggested as a possible cause for brain damage and subsequent ventricular enlargement in schizophrenics (Owen *et al.* 1988), did not account for the variation in response. Previous studies showing that reduced response was related to increased VBR (e.g. Weinberger *et al.* 1980) divided patients into those with and without ventricular enlargement, using mean values from normal controls. Since these values can vary widely, depending on the selection criteria (Smith & Iacono, 1986), such a dichotomy may not be appropriate. Analysis involving VBR as a continuous variable is more valid. The present negative findings do not, of course, rule out the possibility that reduced responsiveness to drugs may be associated with structural changes too subtle to be detected on CT scan.

It should be noted in the present investigation that the VBRs for normal controls are larger than has been reported in other studies (see Smith & Iacono, 1986). Such variation is likely to be due to individual differences in delineating the ventricular outline on CT scans and stresses the importance of 'blind' measurement.

In conclusion, familiality, a history of obstetric trauma or ventricular enlargement were not found to account significantly for variation in the clinical response to antipsychotic drugs among a group of schizophrenic in-patients.

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