British Journal of Psychiatry (1987), **150**, 324–330

Cerebral Ventricular Enlargement in Chronic Schizophrenia: Consistencies and Contradictions

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A study of cerebral ventricular size measured as ventricle to brain ratio (VBR) using computerised tomographic brain scan in chronic schizophrenics provided no support for suggestions that there are significant differences between patients who fall into different clinical subtypes. We found no significant difference in VBR between patients with and without a family history of schizophrenia or between those with or without paranoid symptoms. Applying Crow's classification, contrary to expectations, Type 1 patients had significantly larger ventricles than those with 'mixed' symptomatology (both Type 1 and Type 2 features). We also applied a variety of operational criteria which attempt to define schizophrenia as a whole: of these only Schneider's first-rank symptoms (FRS) yielded conclusive results — FRS-positive patients had significantly larger mean VBR than those without such symptoms. Previously, it has been suggested that ventricular enlargement is more closely associated with 'negative' than with 'positive' symptoms.

Although earlier studies employing lumbar air encephalography produced inconsistent results (Jacobi & Winkler, 1927; Storey, 1966), recent computerised tomographic (CT) scan studies of chronic schizophrenia have been in substantial agreement. Following the first reports by Johnstone *et al* (1976) and Weinberger *et al* (1979) that a proportion of chronic schizophrenics, compared to controls, have enlarged cerebral ventricles, a number of other groups (e.g. Andreasen *et al*, 1982; Nasrallah *et al*, 1982) have confirmed this finding. The percentage of patients with such abnormalities has varied across studies but schizophrenic patient groups consistently show a larger average ventricular size than controls (*Lancet*, 1982), such that this may now be regarded as probably the most replicable biological feature which investigations of the condition have yet revealed.

There is now little dispute about the repeatability and veracity of the finding, but the explanation of ventricular enlargement in schizophrenia is a more contentious issue. The first studies were quickly followed by suggestions that CT scan abnormalities resulted from treatment of schizophrenia or prolonged stays in hospital (Jellinek, 1976; Marsden, 1976). However, subsequent investigations failed to support such a view (Weinberger *et al*, 1979; Tanaka *et al*, 1981). Therefore, most recent interest has centred on more optimistic hypotheses that CT scan abnormalities can tell us something about the aetiology and pathogenesis of schizophrenia, and do not merely reflect secondary consequences of the condition or its treatment.

One of the most provocative hypotheses has been that Johnstone *et al*, 1978). Their observation that ventricular enlargement appeared to be associated with 'negative' clinical features and a degree of cognitive impairment led to the suggestion that CT scan abnormalities provide the structural basis for the 'dementia in dementia praecox'. Subsequently, Crow (1980) proposed that schizophrenia could be divided into two syndromes — a Type 1 characterised by positive symptoms, good response to neuroleptics and probably resulting from abnormalities in brain dopaminergic systems, and Type 2 in which negative symptoms predominate, where response to neuroleptics is less satisfactory and where there is an association with cerebral ventricular enlargement. It was also suggested that in the Type 2 syndrome, ventricular enlargement might be associated with cognitive impairment. Unfortunately, a recent study by members of the same group (Owens *et al*, 1985) failed to show a relationship between ventricular size and cognitive abnormalities. Furthermore, Crow (1980) did not suggest that the two subtypes were necessarily distinct and non-overlapping. Nevertheless there remains considerable interest in such a classification scheme as a starting point for achieving a better understanding of the aetiology of schizophrenia and for deriving an appropriate rationale for the prescription of drugs.

An alternative aetiologically based classification has been put forward by Murray *et al* (1985): the argument is that a genetic contribution is the best established aetiological factor in schizophrenia (Gottesman & Shields, 1982) but a substantial

proportion of schizophrenics have no secondary cases among their relatives. In identical twins discordant for schizophrenia, schizophrenic probands have significantly larger ventricles than the unaffected co-twins and there is a marked tendency for large ventricles to be associated with absence of family history in first-degree relatives (Reveley *et al*, 1984). It was therefore suggested that schizophrenia can be subdivided into a familial form, with normal cerebral ventricles and a presumed genetic aetiology, and a 'non-genetic' or sporadic form, associated with absence of genetic loading, enlarged cerebral ventricles and environmental insult to the brain, e.g. perinatal trauma (Murray *et al*, 1985).

Yet another group were unable to find an inverse relationship between presence of family history and enlargement of cerebral ventricles (Nasrallah *et al*, 1982) but did suggest that CT scan abnormalities might be associated with a more 'traditional' subtypology. The division of schizophrenia into hebephrenic and paranoid categories is notoriously imprecise and unreliable but Tsuang & Winokur (1974) have produced operational definitions of hebephrenic, paranoid and 'undifferentiated' schizophrenic subtypes which greatly improve interrater reliability (McGuffin *et al*, 1984). Applying Tsuang & Winokur (1974) criteria, Nasrallah *et al* (1982) found an association between ventricular enlargement and the paranoid category.

In our study on the CT brain scan appearances of chronic schizophrenics, we considered that each of these systems of the sub-classification merited further attention. However, a further problem is that of how to define schizophrenia as a whole. Operational diagnostic criteria provide a potential 'remedy for diagnostic confusion' (Kendell, 1975) for biological research in schizophrenia but there are now many systems of diagnosis available which show poor agreement one with another (Kendell *et al*, 1979). In the face of such difficulties, Kendell (1983) has suggested a 'polydiagnostic' approach, in which a range of commonly used definitions of schizophrenia are applied to the same set of patients, and the results analysed separately for each. There are two arguments in favour of this. Firstly, no clear-cut and conclusive method exists of deciding whether one set of criteria is 'more valid' than another. Secondly, a polydiagnostic scheme may help decrease disparities in the results of different investigators: (e.g. where investigator 'A' using criteria 'X' produces findings which are at odds with those of investigator 'B' using criteria 'Y'). We therefore decided to assess our patients using an operational criteria checklist composed of items extracted from a variety of commonly used operational diagnostic criteria for schizophrenia and which facilitates polydiagnostic investigation while preserving a satisfactory level of inter-rater reliability (Farmer *et al*, 1983; McGuffin *et al*, 1984).

Subjects and methods

Subjects

Thirty-five patients with a hospital diagnosis of schizophrenia (ICD-295) were selected as representing a series of 'typical' cases of chronic schizophrenia, requiring continued neuroleptic medication to ameliorate or prevent recrudescence of symptoms. All underwent computerised tomographic (CT) brain scanning using a 1010 EMI CT Scanner. The mean age at scan was 37.5 years (s.d. 9.3 years, range 22–57 years). The mean length of illness was 13 years (range 4–22 years).

Clinical assessment and diagnosis

Each subject's age at onset of illness (defined as date of first psychiatric onset) and age at scan was recorded. Duration of illness was calculated as the difference between these two dates. An independent investigator, blind to ventricular size measurements, interviewed the patient and at least one close relative informant to establish the presence or absence of a family history of schizophrenia in first-degree relatives. Where possible, hospital notes of relatives were obtained and examined to confirm diagnosis.

Our operational diagnostic criteria checklist was completed on every patient. This was an expanded version of one previously described (Farmer *et al*, 1983; McGuffin *et al*, 1984), which has been shown to have good item by item inter-rater reliability. The checklist (Appendix 1) was completed for each subject from detailed case records of good standard, which included a personal interview with at least one of the authors. The checklist was then scored dichotomously, as previously described — '0' if the item was absent and '1' if ever present. Where there was dubiety about presence or absence of particular checklist items, the patient was re-interviewed by A. E. F. The checklist data were entered into a computer programme SORT to produce a variety of operational definitions of schizophrenia (Schneider, 1959; Feighner *et al*, 1972; Spitzer *et al*, 1978; Carpenter *et al*, 1973) as previously described (McGuffin *et al*, 1984). In addition, the checklist was expanded slightly, enabling the DSM-III definition to be applied (American Psychiatric Association, 1980) (see Appendix 1). Two of us (A. E. F. and P. McG.) were able to achieve very good inter-rater reliability for DSM-III criteria, using the expanded checklist on a separate series of 20 consecutive admissions with psychotic disorders. ($K = 0.840$, $P = 0.00005$).

Subtyping of the patients into hebephrenic, paranoid and 'undifferentiated' categories was also derived from the checklist scores as previously described (McGuffin *et al*, 1984). In addition we applied a more recently derived method of categorising schizophrenics into categories which we have called 'H Type' (hebephrenic-like) and 'P Type'

https://doi.org/10.1192/bjp.150.3.324 Published online by Cambridge University Press

(paranoid-like) (Farmer *et al*, 1984). Lastly, we wished to divide our patients according to the scheme suggested by Crow (1980) descriptions were cast in an operational format and with his helpful advice we arrived at checklist-based algorithms enabling the separation of schizophrenic patients into Type 1, Type 2 and 'mixed' categories (see Appendix 1). Again we were able to establish excellent inter-rater agreement (K = 0.93, $P = 0.00001$) using a separate consecutive series of admissions.

Assessment of CT scans

The maximum ventricular-brain ratio (VBR) was measured for each scan using a semi-automated method (Reveley, 1985) in which the VBR is measured on the slice with the largest ventricular area. Pixels with a value of 0–25 Hounsfield Units (HU) are considered to represent areas of cerebrospinal fluid (CSF) and those with values from 0–99 HU represent areas of brain plus CSF. A computer count is made of pixels in the ventricular area with a value of 0–25 and of the total number of pixels within the inner table of the skull with a value of 0–99. The VBR (maximum slice) is the ratio (× 100) of these counts.

Results

Mean VBR was 5.88 (s.d. 3.16, range 1.0–15.2). The distribution was positively skewed (skewness 0.85) although when the square root transform for VBR was taken an acceptable Gaussian distribution resulted. Square root transformation of the VBR was therefore used in subsequent analyses. Mean root VBR for 25 male subjects was 2.39, and for 10 female subjects was 2.08. There was no significant difference in ventricular size between the sexes ($t = -1.22$, $P = 0.11$).

There was no significant correlation between VBR and age of illness onset, age at scan or length of illness ($r = 0.15$, 0.13 and 0.01 respectively). Similarly, there was no significant difference in VBR between six (17%) family history-positive subjects and 29 (83%) subjects who had no family history of schizophrenia in first-degree relatives (mean root VBR, family history-positive subjects = 2.17, family history-negative subjects = 2.33; $t = -0.49$, $P = -0.31$).

Table I gives the mean square root VBR and number of subjects in each category for five operational definitions. Schneider's and DSM-III provide dichotomous diagnoses (i.e. 'positive' or 'negative') and non-paired *t*-tests were carried out to compare mean root VBRs for each group. Schneiderian first-rank symptom-positive subjects were shown to have significantly larger mean ventricular size than first-rank symptom-negative subjects ($P = 0.008$). However, DSM-III 'positive' cases were not significantly different from DSM-III 'negative' subjects.

Feighner's, Spitzer's and Carpenter's operational criteria provide a grading of diagnosis. Feighner classifies into 'definite', 'probable' and 'negative' categories, Spitzer into 'broad', 'narrow' and 'negative', and the Carpenter system provides '5-cut off', '6-cut off' and 'negative' categories. One-way analysis of variance was carried out to compare

TABLE I

Operational definition	*No. of subjects*	*Mean root VBR*	*Source*	*One-way analysis of variance: Sum of squares*	*d.f.*	*Mean square*	*F Ratio*	*P*
Feighner								
Negative	8	2.39	Between	3.38	2	1.69	4.29	0.02
Probable	10	1.82	Within	12.58	32	0.394		
Definite	17	2.54						
Carpenter								
Negative	16	2.13	Between	1.12	2	0.59	1.20	0.31
5 cut off	10	2.32	Within	14.84	32	0.46		
6 cut off	9	2.57						
Spitzer								
Negative	6	3.42	Between	0.65	2	0.32	0.68	0.51
Broad	1	1.50	Within	15.31	32	0.48		
Narrow	28	2.30						

Operational criteria		*No. of subjects*	*Mean root VBR*	*Non paired t-test: T*	*d.f.*	*P*
Schneider	Negative	15	1.99	2.53	33	0.0083
	Positive	20	2.54			
DSM-III	Negative	5	2.46	−0.57	33	0.29
	Positive	30	2.27			

https://doi.org/10.1192/bjp.150.3.324 Published online by Cambridge University Press

mean root VBR for each group, for each of the three definitions. The results for Spitzer's and Carpenter's criteria were not significant. Feighner's 'definite' criteria showed significant difference between groups, but Table I shows that the distribution of mean root VBRs is somewhat odd, in that Feighner 'probable' subjects have the smallest mean root VBR, while Feighner 'negative' subjects are intermediate between these two.

Table II shows the number of subjects and mean root VBR for each subtypology. There proved to be no patients of the pure Crow Type 2, using the operational version of the Crow classification. Tsuang & Winokur non-paranoids, Crow Type 1 and Farmer H-type have the largest mean root VBR (2.41, 2.50 and 2.46 respectively) while Tsuang & Winokur paranoid, Farmer P-type and Crow mixed type have the smaller mean root VBR 1.96, 2.13 and 2.09 respectively). Only in the case of the Crow subtypology does the difference in mean root VBR attain statistical significance ($P = 0.04$); however, it is noteworthy that this is in the opposite of the expected direction in that Type 1 patients have a larger mean VBR than do Type 2 patients.

Discussion

Our aim was not to repeat the now well replicated finding that a proportion of schizophrenic patients show enlarged lateral cerebral ventricles, but rather to examine in detail the clinical features which may be associated with ventricular size, in an attempt to establish whether certain symptoms or clusters of symptoms distinguish patients with and without ventricular enlargement. In particular, we were keen to re-assess the claims that certain subtypologies show a relationship with ventricular size. We also aimed to discover whether any of the commonly used and competing operational diagnostic systems offered significant advantage in detecting a form of schizophrenia with a high rate of CT brain scan abnormality.

TABLE II
Ventricular enlargement and subtypes of schizophrenia

		No. of cases	*Mean root VBR*	*P*
Farmer	H-type	18	2.46	N/S
	P-type	17	2.13	(*t*-test)
Crow	Type I	18	2.50	
	Mixed	17	2.09	0.04
	Type II	0	—	(*t*-test)
Tsuang & Winokur (all subjects)	Hebephrenic	6	2.65	NS
	Paranoid	10	2.21	
	Undifferentiated	19	2.24	(Analysis of variance)
Feighner's subjects ($n = 27$)				
Tsuang & Winokur	Non-paranoid	19	2.41	NS
	Paranoid	8	1.96	(*t*-test)

In common with previous groups we obtained a positively skewed distribution of VBRs in our schizophrenic patients, but taking the square root of the results transformed the data to normality and enabled us to use parametric statistics in our analysis. There was no significant correlation between root VBR and age of onset or duration of illness. There was only a small and non-significant correlation between root VBR and age at scan but this is perhaps not surprising in view of the comparative youth of our sample (mean age 37.5 years, maximum age 57 years).

We found no significant difference between the mean VBRs of patients with or without a positive family history of schizophrenia. We thus found no support for the sporadic/familial classification scheme proposed by Murray *et al* (1985). It seems unlikely that our lack of significant difference between the family history-positive and -negative groups is simply due to a Type 2 error and small sample size, since there is not even a trend towards larger cerebral ventricles in the family history-negative group. Indeed, it is the family history-positive schizophrenics who have a slightly larger mean VBR. The division of schizophrenic patients into 'family history-positive' and 'family history-negative' groups is a difficult and unsatisfactory exercise in a number of respects. Firstly, some authors (e.g. Reveley & Chitkara, 1985) take 'family history-positive' to mean a family history of any major psychiatric disorder. However, since the familial diathesis in schizophrenia appears to be fairly specific for schizophrenia and schizophrenia spectrum disorders (Gottesman & Shields, 1982), it seems better to restrict the term 'family history-positive' to those patients who have secondary cases of schizophrenia in their family. Secondly, family history varies according to the quality of available information and the reliability of informants: certainly in our sample we have somewhat more complete information on some families than others. However, since family history was obtained 'blind' to CT scan results, it is unlikely that any bias could have been introduced which would lessen our chance of finding a negative family history-enlarged VBR association. Although one recent study (Turner *et al*, 1986) does support the findings of Reveley *et al* (1984), it is worth noting that most others (Nasrallah *et al*, 1982; Owens *et al*, 1985), in common with ourselves, do not.

On applying the operational checklist version of Crow's (1980) criteria, we were unable to find any pure Type 2 patients. However, nearly half of our subjects (17 out of 35) fell into the 'mixed' category,

showing both Type 2 and Type 1 features. Unexpectedly again, it was the pure Type 1 patients who had the larger mean VBR, with the difference between the two groups (transformed data) being significant at the $P=0.05$ level. It could be argued that the version of the Crow (1980) criteria applied here, although providing good inter-rater reliability, is somewhat oversimplified and we had no specific information about cognitive impairment. The Northwick Park group (Owens *et al*, 1985) and a recent study from Oxford (Kolakowska *et al*, 1985) found no relationship between lateral ventricular size and cognitive impairment. However, it may be that other signs of CNS dysfunction, for example the presence of abnormal movements, are associated with enlarged cerebral ventricles (Owens *et al*, 1985) and such features might properly be incorporated into a revised version of the Type 2 syndrome definition (Crow, 1985).

Our third set of subtypologies were more closely related to traditional categories. Tsuang & Winokur (1975) criteria were applied but our data failed to reveal any significant difference between the hebephrenic, undifferentiated and paranoid categories in respect of ventricular size. Once again, the direction of our findings was the reverse of previously published results. Nasrallah *et al* (1982) found that paranoid schizophrenics had significantly larger ventricles than those who were not of the paranoid subtype. In our series it is the non-paranoid patients who have the slightly larger mean VBR and this applies whether we take the patient group as a whole or only the subset of patients who fulfill the Feighner (1972) criteria for schizophrenia (the latter being the way that Tsuang & Winokur (1975) originally suggested that their criteria be applied). We also used a method of subtyping devised by Farmer *et al* (1984), which although based on multivariate statistical analysis, consists of categories which are somewhat similar to the classical hebephrenic/paranoid classes. There was no significant difference between the groups, but again the H-Type or hebephrenic-like patients showed a slightly larger mean VBR than those of the P-Type or paranoid-like subgroup.

Finally, we examined the VBRs in our patients after classifying them according to a variety of operational diagnostic criteria (Schneider, 1959; Carpenter *et al*, 1973; Feighner *et al*, 1972; Spitzer *et al*, 1978; American Psychiatric Association, 1980). Only the criteria of Feighner *et al* (1972) and Schneider's first-rank symptoms (1959) yielded results which were significant. The Feighner classification allows the separation of patients into definite, probable, and negative (non-schizophrenic) categories. A one-way analysis of variance of root VBR yields significant differences within these groups but the findings are somewhat odd, in that the patients classified as Feighner 'probable' have a lower mean root VBR than the 'negative' or 'definite' groups, whereas, if we were to postulate that the Feighner definition provided a grading either of severity or of certainty of diagnosis, we might have expected the 'probable' category of patient to have a mean VBR which was intermediate between that of the 'negative' and the 'definite' categories. The findings regarding the Schneider criteria are more straightforward, in that there is a highly significant difference between those patients exhibiting first-rank symptoms and those who do not, with the Schneider 'positive' patients having the larger VBRs. Even if we apply a conservative correction factor and multiply the t value by the number of different operational systems used, the difference between the Schneider-positive and Schneider negative patients remains significant at the $P=0.04$ level. This finding is of interest in that several other groups have suggested that large ventricular size is most commonly associated with negative symptoms (Andreasen & Olsen, 1982; Gross *et al*, 1982; Kling *et al*, 1983; Kemali *et al*, 1985; Williams *et al*, 1985) or a Type 2 cluster of symptoms. Here, we have found that it is those patients with classical positive symptoms and those who fall into a Type 1 category who have the larger ventricles.

The subjects described here are in no way an unusual group and were selected specifically as a representative sample of patients with chronic schizophrenia. In the absence of a control group we can make no authoritative statements about which of them are 'normal' or 'abnormal' with regard to ventricular size, and even with access to acceptable controls such separations are somewhat arbitrary (Reveley, 1985). The mean and range of the VBRs in the patients reported here are, however, similar to those in previously described series of schizophrenic patients. Our focus of interest has been entirely upon within-group differences but our analyses provide no support for a consistent relationship between ventricular size and any of a range of clinical subtypes. Our most significant and quite unexpected finding is that in this series ventricular size is associated with the presence of positive symptoms. Inconsistencies and contradictions regarding the clinical features associated with ventricular size are present throughout the recent literature, and it is possible to speculate that technical differences in CT scanning and measurement, and differences in diagnostic criteria or the way that they are applied, play some part. A more fundamental problem may be that most workers have sought to

Coding algorithms[1] for Crow subtypology

Crow Pure Type I	A, B and C required A. One of 26 to 44 = 1 B. 23 = 0 C. 20 = 0
Crow Pure Type II	A, B and C required A. One of 20 = 1, 22 = 1, 23 = 1 B. 26–44 = 0 C. 48 = 0
Crow Mixed Type	A and B required A. One of 26 to 44 = 1 B. One of 20 = 1, 22 = 1, 23 = 1

1. Based on personal advice provided by Dr Crow

Coding algorithm for DSM-III schizophrenia

A, B, C and D required A. One of 7 or 8 = 1 B. 2 and 3 = <45 C. 47 = 1 D. One of 27 to 32, 36 to 39, 41 to 44 = 1 OR one of 18, 19, 20 = 1 AND One of 15, 16, 22, 23, 24 26, 35, 40 = 1

NB Coding algorithms for all other operational definitions previously published (McGuffin *et al*, 1984, Farmer *et al*, 1984)

define categories of patients which differ with respect to a continuous measure of ventricular size such as VBR. No investigators have claimed bi-modality in the distribution of ventricular size and so we might pose the question whether any separation into discrete categories is warranted. However, the presence of bi-modality in itself may be misleading (Murphy, 1964) and a more rational approach to defining subpopulations within schizophrenia with respect to ventricular size might be to carry out an analysis of VBR in patient samples to discover whether the distribution can be more satisfactorily explained by the mixing of two or more curves. The general approach has been outlined (in a somewhat different context) by Everitt (1981) and would seem to be warranted here.

References

AMERICAN PSYCHIATRIC ASSOCIATION (1980) *Diagnostic and Statistical Manual of Mental Disorders* (3rd ed.) DSM-III. Washington DC: Division of Public Affairs, APA.

ANDREASEN, N. C., OLSEN, S. (1982) Negative v. positive schizophrenia. Definition and validation. *Archives of General Psychiatry*, **39**, 789–794.

——, SMITH, M. R., JACOBY, C. G., DENNERT, J. W., OLSEN, S. A. (1982) Ventricular enlargement in schizophrenia: Definition and prevalence. *American Journal of Psychiatry*, **139**, 292–296.

CARPENTER, W. T., STRAUSS, J. S. & BARTOKO, J. J. (1973) Flexible system for the diagnosis of schizophrenia: A report from *Science*, **182**, 1275–1278.

CROW, T. J. (1980) Molecular pathology of schizophrenia: more than one disease process. *British Medical Journal*, **1**, 66–68.

— (1985) The two syndrome concept: origins and current status. *Schizophrenia Bulletin*, **11**, 471–486.

Appendix 1

Operational criteria checklist for schizophrenia

1. Sex	26. Persecutory delusions
2,3. Age of onset	27. Well organised delusions
4. Single	28. Grandiose delusions
5. Unemployed	29. Delusions of influence
6. Illness duration 2 weeks	30. Bizarre delusions
7. Illness duration 6 months	31. Widespread delusions
[1]8. Prodromal/acute/residual symptoms for 6 months	32. Delusions of passivity
9. Poor premorbid work adjustment	33. Primary delusional perception
10. Poor premorbid social adjustment	34. Other primary delusions
11. Pre-existing personality disorder	35. Delusions and hallucinations lasting one week
12. Alcohol/drug abuse within 12 months of onset	[1]36. Persecutory/jealous delusions and hallucinations for one week
13. Family history of schizophrenia	37. Thought insertion
14. Family history of other psychiatric disorder	38. Thought withdrawal
15. Bizarre behaviour	39. Thought broadcast
16. Catatonia	40. Thought echo
17. Speech difficult to understand	41. Third person voices
18. Incoherent	42. Running commentary voices
19. Positive formal thought disorder	43. Abusive/persecutory/accusatory voices
[1]20. Negative formal thought disorder	44. Other non-affective auditory hallucinations
21. Affective symptoms prominent	45. Information not credible
22. Restricted affect	46. Lack of insight
23. Blunted affect	[1]47. Deterioration from premorbid level of functioning
24. Inappropriate affect	[1]48. Schizophrenic symptoms respond to phenothiazines
25. Rapport difficult	

1. Additional items added to checklist to enable DSM-III and Crow operational definitions to be made.

EVERITT, B. S. (1981) Bimodality and the nature of depression. *British Journal of Psychiatry*, **138**, 336–339.

FARMER, A. E., MCGUFFIN, P., SPITZNAGEL, E. L. (1983) Heterogeneity in schizophrenia: a cluster analytic approach. *Psychiatry Research*, **8**, 1–12.

——, MCGUFFIN, P., GOTTESMAN, II. (1984) Searching for the split in schizophrenia: a twin study perspective. *Psychiatry Research*, **13**, 109–118.

FEIGHNER, J. P., ROBINS, E., GUZE, S. B., WOODRUFF, R., WINOKUR, G., MUNOZ, R. (1972) *Archives of General Psychiatry*, **26**, 57–63.

GOTTESMAN, II, & SHIELDS, J. (1982) Schizophrenia. *The Epigenetic Puzzle*. Cambridge: Cambridge University Press.

GROSS, G., HUBER, G. & SCHUTTER, R. (1982) Computerised tomography studies on schizophrenic diseases. *Archive fur Psychiatrie und Nervenkrankheiten*, **231**, 519–526.

JACOBI, A. & WINKLER, H. (1927) Encephalographischen Studien an chronisch Schizophrenen. *Archiv fur Psychiatrie und Nervenkrankheiten*, **81**, 299–332.

JELLINEK, E. H. (1976) Cerebral atrophy and cognitive impairment in chronic schizophrenia. *Lancet*, **2**, 1202–1203.

JOHNSTONE, E. C., CROW, T. J., FRITH, C. D., HUSBAND, J., KREEL, L. (1976) Cerebral ventricular size and cognitive impairment in chronic schizophrenia.

——, ——, ——, STEVENS, M., KREEL, L., & HUSBAND, J. (1978) The dementia of dementia praecox. *Acta Psychiatrica Scandinavica*, **57**, 305–324.

KEMALI, D., MAI, S., GALDERISI, S., ARIANO, M. G., CESARELLI, M., MILICI, N., SALVATI, A., VALENTE, A. & VALPE, M. (1985) Clinical and neuropsychological correlates of cerebral ventricular. *Journal of Psychiatric Research*, **19**(4), 587–596.

KENDALL, R. E. (1975) The role of diagnosis in psychiatry. Oxford: Blackwell Scientific Publications.

—— (1982) The choice of diagnostic criteria for biological research. *Archives of General Psychiatry*, **39**, 1334–1335.

——, BROCKINGTON, I. F., LEFF, J. P. (1979) Prognostic implications of six alternative definitions of schizophrenia. *Archives of General Psychiatry*, **36**, 25–31.

KLING, A. S., KURTZ, N. TACHINI, K. & ORZECK, A. (1983) Ct scans in sub-groups of chronic schizophrenics. *Journal of Psychiatric Research*, **17**(4), 375–384.

KOLAKOWSKA, T., WILLIAMS, A. W., JAMBOR, K. & ARDERN, M. (1985) Schizophrenia with good and poor outcome. III Neurological 'soft' signs, cognitive impairment and their clinical significances. *British Journal of Psychiatry*, **146**, 348–357.

LANCET (1982) Editorial: The CT scan in schizophrenia. *Lancet ii*, 968.

MARSDEN, C. D. (1976) Cerebral atrophy and cognitive impairment in chronic schizophrenia. *Lancet*, **ii**, 1079.

MCGUFFIN, P., FARMER, A. E., GOTTESMAN, I. I., MURRAY, R. M., REVELEY, A. M. (1984) Twin concordance for operationally defined schizophrenia. *Archives of General Psychiatry*, **41**, 541–545.

MURPHY, E. A. (1974) One cause? Many causes? The argument from the bimodal distribution. *Journal of Chronic Diseases*, **17**, 301–324.

MURRAY, R. M., LEWIS, S. W., REVELEY, A. M. (1985) Towards an aetiological classification of schizophrenia. *Lancet*, **ii**, 1023–1026.

NASRALLAH, H. A., CHARLES, G. J., MCCALLEY-WHITTERS, M. & KUPERMAN, S. (1982) Cerebral ventricular enlargement in subtypes of chronic schizophrenia. *Archives of General Psychiatry*, **39**, 774–777.

OWENS, D. G. C., JOHNSTONE, E. C., CROW, T. J., FRITH, C. D., JAGOE, J. R. & KREEL, L. (1985) Lateral ventricular size in schizophrenia: relationship to the disease process and its clinical manifestations. *Psychological Medicine*, **15**, 27–41.

REVELEY, M. A. (1985) Ventricular enlargement in schizophrenia. *British Journal of Psychiatry*, **146**, 367–371.

——, CHITKARA, B. (1985) Letter to Editor. *Lancet*, June 29, 1503.

REVELEY, A. M., REVELEY, M. A., MURRAY, R. M. (1984) Cerebral ventricular enlargement in "non-genetic" schizophrenia: a controlled twin study. *British Journal of Psychiatry*, **144**, 89–93.

SCHNEIDER, K. (1959) *Clinical psychopathology*. Translated by M. Hamilton, New York: Grune & Stratton.

SPITZER, R. L., ENDICOTT, J., ROBINS, E. (1978) *Research Diagnostic Criteria*. Instrument No 58. New York: New York Psychiatric Institute.

STOREY, P. B. (1966) Lumbar air encephalography in chronic schizophrenia: a controlled experiment. *British Journal of Psychiatry*, **112**, 135–144.

TANAKA, T., HAZAMA, H., KAWAHARA, R. & KOBAYASHI, K. (1981) Computerised tomography of the brain in schizophrenic patients. *Acta Psychiatrica Scandinavica*, **63**, 191–197.

TSUANG, M. T., WINOKUR, G. (1974) Criteria for subtyping schizophrenia. *Archives of General Psychiatry*, **31**, 43–47.

TURNER, S., TOONE, B., BRETT-JONES, A. (1986) Computerised tomography scan changes in early schizophrenia — preliminary findings. *Psychological Medicine*. (In press).

WEINBERGER, D. R., TORREY, F. E., NEOPHYTIDES, A. N., & WYATT, R. J. (1979) Lateral cerebral ventricular enlargement in schizophrenia. *Archives of General Psychiatry*, **36**, 735–739.

WILLIAMS, A. O., REVELEY, M. A., KOLAKOWSKA, T., ARDERN, M. & MANDELBROTE, B. M. (1985) Schizophrenia with good and poor outcome: II. Cerebral ventricular size and its clinical significance. *British Journal of Psychiatry*, **146**, 239–246.

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