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Lecture

Is There Really A Split In Schizophrenia?
The Genetic Evidence

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Although the clinical presentation and course of schizophrenia is highly variable, it is unclear whether this reflects heterogeneity at an aetiological level. The genetic evidence is reviewed concerning 'traditional' clinical subtypes as well as more novel categories derived from multivariate statistical methods and Crow's type I-type II classification. Recent data based on a twin series and re-analysis of older published family material suggest that attempts to divide up schizophrenia have resulted in splits between two or more categories of disorder which occupy different positions on the same continuum of liability. Thus, apparent heterogeneity is more likely to be due to quantitative difference in familial-genetic loading rather than qualitative differences. Similarly, the hypothesis that schizophrenia can be broadly divided into two groups, one genetic and the other non-genetic has little to support it. It seems improbable that any further useful and genetically relevant subdivision of schizophrenia can be effected on purely clinical grounds. Further progress awaits developments in the discovery of endophenotypes and the application of molecular genetic marker strategies.

Current concern with categories such as 'type I' and 'type II' (Crow, 1980), positive-symptom versus negative-symptom (Andreasen, 1985; Pogue-Geile & Harrow, 1985) and 'sporadic' versus familial schizophrenia (Murray *et al*, 1985) represents a new and interesting phase in an old and unresolved debate over the unity and diversity of the disorder (*British Medical Journal*, 1969; Farmer *et al*, 1984). E. Bleuler (1911) introduced the term 'schizophrenia' to cover *a group* of disorders which Kraepelin (1896) had implied could be comfortably subsumed under a single category. Many researchers since, impressed by the clinical variety of patients described as 'schizophrenic', have taken a Bleulerian stance and have aimed to be splitters rather than Kraepelinian lumpers of the syndrome.

Psychiatric geneticists and biological psychiatrists, in particular, have been on the side of the splitters. The case was put authoritatively and succinctly by Eliot Slater in a paper written nearly 40 years ago (Slater, 1947). He wrote: "In view of the fact that schizophrenia is a good deal more common than any single genetically determined disorder is otherwise known to be, heterogeneity is inherently probable".

Our purpose, therefore, in this article is to review both the older and more recent genetic evidence concerning heterogeneity in schizophrenia and to decide whether it supports the widely held point of view that we are dealing with several, perhaps many conditions.

On lumping and splitting

In his encyclopaedic catalogue of mendelising genetic disorders McKusick (1983) favours the view that what is called 'schizophrenia' is a mixture of different entities. However, elsewhere he points out (McKusick, 1969) that the leading principles of genetic nosology include not only the idea of heterogeneity, but also of pleiotropism. Pleiotropism is the phenomenon of a single aetiological factor (for example a single gene) having multiple effects. A nice example with psychiatric relevance is the demonstration by Penrose (1952) of the various (biochemical, morphological and behavioural) phenotypic manifestations of the phenylketonuria gene. However, we can broaden the notion of pleiotropism to include non-genetic medical conditions and here syphilis and systemic lupus erythematosis provide excellent examples of how a specific pathogenic process can have clinical manifestations which are many and various, often leading to diagnostic error and perplexity.

In cases of late syphilis the contrasts in presentation between one patient and another may be quite

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disparate, whereas in psychiatry classification and differentiation of syndromes is based on comparatively subtle differences, and moreover on differences which are liable to change over time. We therefore ignore at our peril McKusick's (1969) warning that when dealing with heterogeneity, purely phenotypic differences may provide "the most treacherous basis for decision". Against this, it must be allowed that progress in medicine has depended to a large extent on teasing apart broad clinical syndromes and on the delineation of specific, narrower disease entities. Little more than a century ago conditions such as 'dropsy' and anaemia were considered adequate diagnostic entities which were only subsequently separated by a combined process of refining clinical descriptions and pursuing all available clues concerning aetiologies and pathogeneses. In schizophrenia the pathogenesis remains obscure but there is compelling evidence of an important genetic contribution to the aetiology (Gottesman & Shields, 1982). Indeed if we are to start by lumping all of the conservatively diagnosed Western European studies of schizophrenia together, genes probably account for about two-thirds of the variation in liability to the disorder (Gottesman & Shields, 1967; McGuffin, 1984; McGue *et al*, 1985). Clinical heterogeneity in schizophrenia undoubtedly exists but it is only of limited interest if this does not reflect *aetiological* heterogeneity. Therefore whether there is a genetic split (or set of splits) in schizophrenia might be viewed as the most important current issue in the nosology of the syndrome.

Clinical and 'traditional' subtypes

Family data

Leonhard (1959) has provided probably the most elaborate and extensive scheme for splitting schizophrenia on the basis of descriptive psychopathology. Other workers, particularly those in the Soviet Union, have devised different schemes largely based on course and outcome (Snezhevnevsky, 1968). However, such complicated approaches have not won widespread acceptance and most twin and family researchers have adopted more time-honoured subtypologies largely based on Kraepelinian–Bleulerian categories. Particular attention has been focused on a paranoid versus hebephrenic (or paranoid versus non-paranoid) classification. The largest single dataset concerned with schizophrenic probands and their families is that of Kallmann (1938). By modern standards there are a number of methodological deficits. These include diagnoses in relatives which were mainly not made blind to proband information, an absence of explicit diagnostic criteria, and a lack of a suitable control group.

Nevertheless, the sample size and the wealth of detail provided encourages our close attention. Kallmann (1938) was himself unimpressed by the degree of familial homotypia in his material, i.e. the tendency for affected pairs of first-degree relatives to belong to the same subtype of schizophrenia. He pointed out that only in about 70% of affected relative pairs was the subtype identical. However, Slater (1947) subsequently retabulated Kallmann's data and performed a χ^2 analysis which showed that the tendency for like to go with like in parent–offspring pairs classified as hebephrenic, catatonic and paranoid, occurred at the 0.01 level of significance. There have been at least eight other studies (reviewed by Kendler & Davis, 1981) which have addressed much the same question. Most have shown a tendency for paranoid versus non-paranoid schizophrenia to 'breed true'. Only three comparatively recent studies (Tsuang *et al*, 1974, 1980; Scharfetter & Nusperli, 1980) carried out diagnosis of relatives blind to the proband subtype. Two of these studies (Tsuang *et al*, 1974; Scharfetter & Nusperli, 1980) found a tendency towards homotypia which in the latter study (1980) occurred at a better than chance level. However, the more recent study of Tsuang *et al* (1980) used narrow operational criteria (Tsuang & Winokur, 1974) to define a paranoid subtype and not only found absence of homotypia but also a tendency at long-term (30–40 years) follow-up for paranoid schizophrenia to progress to a hebephrenic or 'undifferentiated' picture.

A rather different way of examining family data is to concentrate on quantitative rather than qualitative differences between subtypes. Thus if we divide up probands according to subtype but simply examine the frequency of schizophrenia among relatives irrespective of subtype there is a fairly consistent pattern in nearly all studies in that the relatives of patients with paranoid schizophrenia tend to show a lower morbid risk for all types of schizophrenia than do the relatives of patients with non-paranoid or hebephrenic disorders. Kendler & Davies (1981) have suggested that this is sometimes an artefact of the method of age correction. The simplest and commonest method of age correction is the shorter (or abridged) Weinberg method (Slater & Cowie, 1971; McGuffin, 1984a). Here it is assumed that there is a (more or less) well-defined period of risk for acquiring a disorder and by a simple method of weighting of those relatives who have not lived through this period an adjusted denominator is calculated to estimate the life time expectancy (or morbid risk) of disorder. Kendler & Davies argue that if the period of risk is assumed to be the same for all subtypes of disorder then the rates in

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relatives of older, later onset cases such as paranoid schizophrenics will tend to be underestimated. However, this bias cannot account for all the differences in the literature. For example, in Kallmann's (1938) study the differences in the frequency of schizophrenia in relatives of index cases which 'nuclear' (hebephrenic and catatonic) versus 'peripheral' (paranoid and simple) disorders are apparent even in the non-age corrected data.

Twin studies

The available twin data is mainly in keeping with the family findings. Kringlen (1967) and Fischer (1973) showed that in monozygotic twins, there was virtually complete homotypia for subtype in twin pairs concordant for schizophrenia. However, co-twin assessment was not, however, performed blind to that in the proband. This was rectified in the study of Gottesman (1968) where there was again a marked tendency toward subtype concordance even though diagnosis was here made blindly. One of the drawbacks of these earlier studies, as with the earlier family data is that they were carried out without using explicit operational criteria. We have therefore reexamined the Maudsley twin series originally studied by Gottesman & Shields (1972) and have applied the subtyping criteria of Tsuang & Winokur (1974) to the detailed case abstracts. In our hands these criteria have been found to provide very good inter-rater reliability (Farmer *et al*, 1983; McGuffin *et al*, 1984). The results of the subtyping of the twin material are shown in Table I. In common with previous investigators we find a marked tendency toward subtype concordance. However, this is not complete in the monozygotic (MZ) sample and it is apparent that when the proband has a non-paranoid form of disorder we obtain higher concordance rates for schizophrenia as a whole than when the proband has a paranoid condition. This is therefore in good agreement with the results reported by Gottesman (1968) and by Kringlen (1967) both of whom found a similar pattern and hints that the distinction between paranoid and other forms of schizophrenia is quantitative rather than qualitative.

TABLE I
Probandwise concordance in the Maudsley (1948–1964) Schizophrenic Twin Series

Subtypes of Tsuang & Winokur (1974) *Concordance for*	*MZ*	*%*	*DZ*	*%*
Schizophrenia, where proband is:				
Paranoid	2/5	40	1/14	7
Non-paranoid (hebephrenic and 'undifferentiated')	13/21	62	3/20	15
Subtype, where both twins are diagnosed schizophrenic	13/15	87	3/3	100

MZ = monozygotic, DZ = dizygotic.

Explanatory models

The transmission of schizophrenia is best considered in terms of liability/threshold models (Falconer 1965; Gottesman & Shields, 1967; Reich *et al*, 1972). Clearly schizophrenia does not show a typical Mendelian pattern of segregation and *discordance* of over 50% in pooled data from recent series of identical twins (Gottesman & Shields 1972) is sufficient evidence that environmental as well as genetic factors are involved. 'Liability' is considered to be a continuously distributed variable in the general population which is determined by both genes and environment (acting in a predominantly additive fashion) such that only those individuals whose liability exceeds a certain threshold value at some point in time, manifest the disorder. Single major locus models, where a single gene is the sole source of familial liability have been shown to be inadequate in explaining the familial aggregation of schizophrenia as a whole (O'Rourke *et al*, 1982). It seems more likely that in schizophrenia we are dealing with many genes at different loci acting in a mainly additive way (Gottesman & Shields, 1967) or possibly a major gene against a polygenic background (McGue *et al*, 1985). Reich and his colleagues (1972, 1979) have extended Falconer's (1965) original single threshold model to include disorders which occur in two or more forms. It is assumed that liability is normally distributed (or could be transformed to normality) and that those individuals who lie beyond a first threshold will show a 'broad', milder form of the disorder while those beyond a second, more extreme, threshold will show a 'narrow', more severe form. Relatives of affected individuals will show a mean liability which is greater than that of the general population and thus more will lie beyond the threshold for being affected. The 'isocorrelational' version of the model (Reich *et al*, 1979) predicts that the mean liability of relatives of 'narrow' cases will be greater than that of 'broad' cases. The model is illustrated in a somewhat simplified form in Fig. 1. Thus in schizophrenia we might consider schizophrenia-as-a-whole as a 'broad' form, with non-paranoid (or hebephrenic or 'nuclear') categories as a narrow form, and paranoid schizophrenia as 'broad-but-not-narrow' category.

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TABLE II
A reanalysis of Kallmann's (1938) family study of schizophrenia

Proband subtype	*Class of relative*	*Total at risk (BZ)*	*Relatives*		
			% Affected	*Observed n affected*	**Expected n*
Peripheral (paranoid or simple)	Children	307	9.1	28	32.5
Nuclear (hebephrenic or catatonic)	Children	373	17.7	66	63.9
Peripheral (paranoid or simple)	Siblings	739	6.2	46	39.6
Nuclear (hebephrenic or catatonic)	Siblings	1257	8.2	103	106.1

*Expected *n* affected under two threshold 'isocorrelational' models (Reich *et al*, 1979) where nuclear schizophrenia = 'narrow' from disorder and peripheral schizophrenia = 'broad-but-not-narrow' form assuming population morbid risk of broad form (K_pB) = 1%, $\chi^2 = 0.332$, ld.f. (NS), parameter estimates: $r_c = 0.524$, $r_s = 0.361$, $K_pN = 0.54\%$.

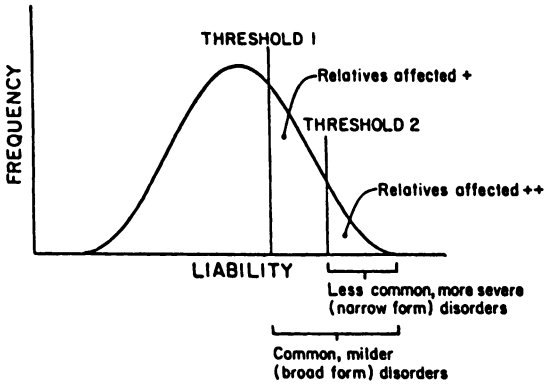


FIG. 1 Two-threshold multifactorial model.

As an illustrative example we have attempted to fit a model of this type using Kallmann's (1938) data (Table II). This was carried out using a FORTRAN computer program, TETCOR, where the best fit is found iteratively by minimising a χ^2 function using the MINUIT optimisation routine (CERN, 1974). We have assumed that population morbid risk of the broad form (K_pB) is 1% and we have employed the program to calculate the best fit values of the remaining parameters, comprising the population morbid risk of the narrow form (K_pN) and the correlations in liability. As we can see from Table II, if we allow different correlations in liability for parent–offsprint (r_c) and sibling–sibling (r_s) pairs we obtain an excellent fit (cf. Barn, 1982). We have not attempted a similar model-fitting procedure on the other smaller datasets but as we have already commented the overall pattern in most of these is similar. We therefore consider that most of the family and twin evidence on the transmission of 'traditional' subtypes of schizophrenia is in keeping with the notion of differing thresholds on a single continuum of liability rather than of the existence of qualitatively distinct subentities.

Statistically derived subtypes

As instruments with which to 'carve nature at the joints' multivariate statistical methods have found favour in studies of affective disorder (Kendell, 1975; Paykel, 1981) but have been much less popular in schizophrenia research. Some investigators have attempted to use cluster analytic methods for defining subtypes within the schizophrenia syndrome (e.g. Strauss *et al*, 1973; Bartko *et al*, 1981) but only one group (Farmer *et al*, 1983, 1984) have viewed their results from a specifically genetic perspective. Farmer *et al* (1983) applied two mathematically different methods of cluster analysis to data on chronic schizophrenics. The variables used were from a comprehensive checklist of symptoms derived from commonly used operational diagnostic criteria. Two fairly distinct clusters were derived and there was surprisingly good agreement between the two clustering programmes. Simulation studies indicated that the level of agreement would occur by chance less than once in a hundred. The clusters remained stable when extra cases were added. Furthermore, where index cases and their schizophrenic relatives were assigned to subgroups the level of homotypia was significantly better than chance expectation.

Subsequently the characteristics of the groups were further explored using discriminant analysis (Farmer

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TABLE III
Probandwise concordance in the Maudsley (1948–1964) Schizophrenic Twin Series

Subtypes of Farmer et al *(1983, 1984) Concordance for*	*MZ*	*%*	*DZ*	*%*
Schizophrenia where proband is:				
P-type	4/12	33	1/17	6
H-type	11/14	79	3/17	18
Subtype, where both twins are diagnosed schizophrenic	11/15	73	4/4	100

MZ = monozygotic; DZ = dizygotic.

et al, 1984). Because of their resemblance to some descriptions of more 'traditional' subtypes the group with onset before 25 years, poor premorbid work adjustment and such clinical features as blunting of affect, thought insertion and third-person auditory hallucinations was named hebephrenic-like or 'H-type', while the group with later onset, poor premorbid *social* adjustment and well organised delusions was named paranoid-like or 'P-type'. Using discriminant function scores the twins from the Gottesman & Shields (1972) study were assigned to H- and P-subtypes and the concordance examined (Table III), a pattern very similar to that for the Tsuang & Winokur (1974) criteria emerged. That is, there is a tendency towards homotypia, which is nevertheless incomplete in genetically identical twins. But when subtype in co-twins is ignored and only concordance rates for schizophrenia as a whole considered according to whether the proband is H- or P-type, and the co-twins of H-type probands have higher rates of schizophrenia than do the co-twins of P-type probands. The findings are therefore suggestive once more of a quantitative rather than a qualitative distinction. Although no formal model fitting has been attempted it might be again postulated that H-type schizophrenia is but another narrow-form disorder with P-type schizophrenia a broad-but-not-narrow form.

Type I, type II and negative symptom schizophrenia

A finding which has achieved a high level of consistency across different centres is of enlarged lateral cerebral ventricles on the computerised tomographic (CT) brain scans of a proportion of schizophrenics. This was first reported by Johnstone and colleagues (1976) and has been replicated in nearly all subsequent studies (Reveley, 1985) (however, the recent criticisms of Smith & Iacono (1986) regarding schizophrenia/control comparisons must be noted). The finding of ventricular enlargement has caused renewed interest in what Johnstone *et al* (1976) have termed the 'dementia of dementia praecox'. Crow (1980) has proposed that there may exist two syndromes, a type I disorder, characterised by positive symptoms and responsiveness to neuroleptics, while a type II syndrome is more closely associated with negative symptoms, poor response to treatment and perhaps with cognitive impairment and morphological changes reflected in CT brain scans. Crow suggested (1980) that although the syndromes overlap to a considerable extent, the type I disorder is likely to be associated with abnormal dopaminergic mechanisms while the type II disorder would have some other (perhaps viral-infective) pathology. We have attempted with author's guidance to cast Crow's (1980) clinical criteria in an operational format to facilitate investigation of genetic aspects of this subtypology and have been able to demonstrate good inter-rater reliability using this approach (Farmer *et al*, 1987).

As with other subtyping systems described above we have reexamined the clinical abstracts for the Gottesman & Shields (1972) schizophrenic twin series and have reclassified affected individuals (Table IV). Pure type II cases are rare in this series but once again we see a tendency towards homotypia which is incomplete. Furthermore, there is some suggestion that the mixed form is a 'more genetic' condition than is type I schizophrenia in that there is a very marked difference between MZ and DZ concordance rates where the proband has a mixed type disorder.

Unfortunately such a small amount of data does not permit any definite conclusions about the Crow subtypology and we are unaware of any other familial

TABLE IV
Probandwise concordance in the Maudsley (1948–1964) Schizophrenic Twin Series

Subtypes of Crow (1980) Concordance for	*MZ*	*%*	*DZ*	*%*
Schizophrenia, where proband is:				
type I	8/15	53	4/21	19
Mixed type	7/11	64	0/11	0
Type II	0/0	0	0/2	0
Subtype, where both twins are diagnosed schizophrenic	11/15	73	3/4	75

MZ = monozygotic, DZ = dizygotic.

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data which might help clarify the issue. Furthermore, as a result of the CT scan studies of the Northwick Park group, Crow's own views on what forms the most useful clinical basis for a type I–type II separation are evolving and changing (Crow, 1985).

There is, however, some evidence which has a bearing on a related concept, that of a separation of schizophrenia into two groups on the basis of whether negative or positive symptoms predominate. Dworkin & Lenzenweger (1984) have examined the available published extracts from systematic twin studies. Using their own unpublished system, which they find to be reliable in rating the presence of negative symptoms, they were able to divide up probands from monozygotic pairs into 'high negative' and 'low negative' categories. A fairly consistent picture emerged, with all twin studies, except for that of Kringlen (1967) showing higher concordance where the proband exhibited a high rate of negative symptoms. This approach is rather different from and considerably simpler than the Crow subtypology. Nevertheless, there is clearly a resemblance between these results and those of our own efforts to apply the operationalised Crow criteria to the Maudsley schizophrenic twin series.

It is therefore tempting to speculate that in separating off a group of patients with type II mixed, or predominantly negative symptoms, we are simply selecting a more severely affected group which, as with non-paranoid, hebephrenic or 'H-type' cases tend to occupy a more extreme position on a continuum of liability. It might be argued therefore that all of these findings are reminiscent of the earlier work of Gottesman & Shields (1968, 1972) who took a more straightforward approach to the question of severity. The probands from identical twin pairs were divided according to time spent in hospital. Where the proband had spent less than 2 years in hospital there was a concordance of only 27% as against a rate of 77% where a proband had spent more than 2 years in hospital since the onset of his/her illness. Similarly, where the proband had shown an inability to stay out of hospital for at least 6 months since the onset of their disorder, the rate of schizophrenia in the co-twins was 75%.

Non-genetic schizophrenia?

The evidence considered thus far would seem to favour the existence of 'more genetic' and 'less genetic' varieties of schizophrenia lying on the same continuum with cut-off points dependent on chosen clinical criteria. A more radical suggestion has recently been put forward by Murray *et al* (1985), that 'sporadic' or non-genetic forms of schizophrenia may be quite common and that presence or absence of a family history of the disorder provides a useful starting point for such a classification scheme. There are undoubtedly many organic conditions which can present with a schizophrenic like disorder (Davison & Bagley, 1969; Propping, 1983) but well-established cases of 'symptomatic' schizophrenia which, from a genetic viewpoint, might be considered as 'phenocopies' are uncommon in clinical practice. Murray and his colleagues (1985) suggest that sporadic cases of schizophrenia may be commoner than are generally supposed and that the environmental causes most often go undetected. They point out that identical twins discordant for schizophrenia show marked differences in cerebral ventricular size measured on CT brain scans. Although the numbers involved were small Reveley *et al* (1982) found significant tendency for the affected proband to have larger ventricles than the non-schizophrenia co-twin. It was postulated that this might reflect early trauma such as birth injury, and a subsequent study (Reveley *et al*, 1984) found a relationship between enlarged cerebral ventricles, negative-family history of psychiatric illness and positive history of early cerebral insults in schizophrenic twins. However, it should be noted that 'family-history negative' here meant absence of illness in relatives other than the co-twin so that the sample of 'family history negative' probands appears to have included some individuals with affected co-twins. Thus the apparent elegance and simplicity of a family-history positive/family-history negative division may be dangerously deceptive.

There are a number of general objections to a family-history positive/family-history negative split. First, any plausible model of transmission (McGue *et al*, 1985) would predict that those patients without a family history of schizophrenia would comprise a high proportion of genetic cases who are 'chance isolates' (Elandt-Johnson, 1971) as well as those who are true non-genetic cases. However, there would be no straightforward way of differentiating between the two. Second, the chances of obtaining a positive family history of psychiatric disorder are closely related to the quality of information available. Thorough family interview studies inevitably uncover more secondary cases among relatives than do studies based on history alone. Third, the proportion of family-history positive cases must also depend on family size and on the proportion of relatives who have passed through the age of risk. Most authors agree that there is an increased rate of schizophrenia and of 'spectrum' disorders among the relatives of schizophrenia rather than an increase in psychopathology generally (Gottesman & Shields, 1982). Nevertheless, Reveley *et al* (1984) have taken a broad

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perspective on what constitutes a 'family-history positive' case and include a family history of *any* major psychiatric disorder is about 10% (and recent studies suggest that this is a conservative estimate (Sturt *et al*, 1984; Helzer *et al*, 1985)) then we would obtain a distribution of family-history positive cases by chance alone like that shown in Table V. Obviously this is not entirely realistic since it does not take into account the tendency of most psychiatric disorders to aggregate in families (McGuffin, 1984). However, the table serves to illustrate that family size cannot be ignored as a potential confounding variable in studies of this type.

TABLE V
Proportion of a population expected to be family-history positive for a 10% trait by chance

*Proportion (%)**	*Number of relatives*
10	1
19	2
27	3
34	4
41	5
47	6
52	7

*proportion, p, calculated as $p = 1-(1-\pi)^n$
where π = population frequency and n = number of relatives

A more direct criticism of the hypothesis of Murray *et al* (1985) is that we might expect to see a consistent relationship between presence or absence of family history and cerebral ventricular size in other studies of schizophrenics. However, as Table VI shows, there is a disappointing lack of agreement between studies carried out in different centres. Some (e.g. Turner *et al* 1986) support Murray's hypothesis; one (Nasrallah *et al*, 1982) produced findings in the opposite direction of that predicted, while most others actually find no significant differences between the family-history positive and family-history negative groups. This is perhaps not surprising in the light of the recent analysis presented by Eaves *et al* (1986) which demonstrated that the discriminatory power of a familial/non-familial distinction is actually very low.

Do earlier twin or family studies provide any clarification? Only a minority of even the most thoroughly investigated schizophrenics have secondary cases in their first- or second-degree relatives and over 60% must be classified as 'family-history negative' (Bleuler, 1978). Given that this is so, it could be asked whether discordance in identical twins might be due to an admixture of genetic and

TABLE VI
CT brain scan studies VBR in family-history positive (FHP) vs family-history negative (FHN) schizophrenics

Authors	*Summary of finding*
Reveley *et al* (1984)	Mean VBR in FHN twins significantly *greater* than in FHP twins
Nasrallah *et al* (1982)	Mean VBR in FHN patients significantly *less* than in FHP patients.
Owen *et al* (1985)	More FHP than FHN patients with VBR greater than control mean.
Farmer *et al* (1985)	No significant difference between FHP and FHN patients.
Williams *et al* (1985)	
Reveley & Chitkara (1985)[1]	
Turner *et al* (1986)	Mean VBR in FHN patients significantly *greater* than in FHP patients.

1. One-way anova showed significant differences with VBR in FHN patients > VBR in FHP patients > VBR in controls.

non-genetic cases. The question was first investigated by Luxenburger (1928). He found that discordant pairs had other affected family members as often did concordant pairs, results which were subsequently replicated by other investigators (Kringlen, 1967). Furthermore, a study of the adult offspring of MZ twins discordant for schizophrenia revealed a similar morbid risk for the disorder in both the children of the schizophrenic probands and the children of the non-schizophrenic co-twins (Fischer, 1971). (The latter finding has been confirmed and extended in the offspring of MZ and DZ twins by Gottesman & Bertelsen (in preparation)). Both findings strongly suggest that a genetic/sporadic admixture hypothesis to explain discordance for schizophrenia in identical twins is incorrect but supports the idea that 'sporadic' or non-genetic forms of schizophrenia are uncommon. This being so, the studies of discordant twins should provide an ideal means of pinpointing specific environmental stressors which may precipitate the disorder in the genetically susceptible as well as indicating possible protection factors. Unfortunately, results from older studies are disappointingly inconsistent. Pollin & Stabenau (1968) are often quoted as finding that in discordant MZ pairs the schizophrenic index case was more likely to have had a history of birth trauma and low birth weight and to have had a submissive dependent premorbid personality than his unaffected co-twin. Other studies provide some support regarding premorbid personality factors but despite evidence of the general role of birth trauma (McNeill & Kaij, 1978) there has been no convincing replication of the *specific* birth history findings (Gottesman & Shields, 1982).

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Biological and genetic markers

Thus far, we have mainly discussed subcategories based upon clinical signs and symptoms, or what Gottesman & Shields (1972) have called 'exophenotypes'. It might be hoped that the discovery of biological markers or 'endophenotypes' for schizophrenia might take us a step nearer toward primary gene products and facilitate less ambiguous methods of classification (McGuffin, 1984*b*). Attempts to subclassify schizophrenics according to biological criteria have been reviewed by Meltzer (1979) but there is, for the most part, a disappointing inconsistency in results. The biochemical marker which has perhaps excited the most attention and which may be of genetic relevance is platelet monoamine oxidase (MAO). Potkin *et al* (1978) reported that platelet MAO activity was significantly lower in paranoid than in non-paranoid schizophrenic patients. Unfortunately, other groups, (e.g. Meltzer *et al*, 1980) have been unable to replicate this finding and the weight of evidence from other studies (reviewed by Kendler & Davis, 1981) does not favour a clear separation of groups of schizophrenics on the basis of platelet MAO activity. Further doubt concerning the usefulness of MAO as a marker derives from the studies of Rice *et al* (1982, 1984) which suggest that platelet MAO is controlled by a single major locus but that the less common of its two alleles is the one coding for *high* MAO activity and that the vast majority of the population, over 90%, carry at least one 'low MAO' gene. Clearly there is some difficulty in reconciling this finding with suggestions that platelet MAO may be a marker for schizophrenia, a disorder where the lifetime incidence in the population is 1% or less.

Genetic markers are a special category of biological marker. Although still often used in a rather broad sense in the psychiatric literature (e.g. Shuckitt, 1986) the term genetic marker is probably best restricted to cover traits which have a simple mode of inheritance and which are demonstrably polymorphic (i.e. where there are two or more alleles with a gene frequency of at least 1%) (Giblett, 1969). The better known genetic markers include red cell groups such as ABO, rhesus, MN and soon as well as major histocompatibility (HLA) antigens, various blood protein polymorphisms and red cell enzymes. In addition to these 'conventional' markers the advent of 'the new genetics' of recombinant DNA (Emery, 1984) has meant that many more genetic markers are now available and that the day is not far off when the human genome (i.e. the set of 22 pairs of autosomes and two sex chromosomes) will be extensively mapped. So far over 900 genes have been assigned to chromosomal locations (De La Chapelle, 1985), but only about 25% of genes so far mapped are detectably polymorphic (*American Journal of Human Genetics*, 1983) and only a proportion of these have been investigated in relation to schizophrenia (see recent review by McGuffin & Sturt, 1986).

Possible associations discovered by recent population studies involving blood complement factors (Rudduck, 1985) merit further investigation, but most genetic marker findings in schizophrenia to date have been disappointingly inconsistent and convincing replications of positive findings have been rare. A notable exception is the evidence concerning the HLA system and subtypes of schizophrenia.

Associations between certain specificities of the HLA system and a number of common diseases are now well established (Thomson, 1981). Such disorders include juvenile diabetes, multiple sclerosis and ankylosing spondylitis. Most HLA associated diseases are not rare have a tendency to run in families, but show complex patterns of inheritance which are not classically Mendelian. Not surprisingly, therefore, schizophrenia came under scrutiny not long after the first HLA-disease reports (Cazzulo *et al*, 1974; Eberhard *et al*, 1975). However, studies of schizophrenia as a whole provided no clear pattern of association across different centres (McGuffin, 1979). It was only when schizophrenia was broken down into possible subtypes that a more consistent set of results emerged. In particular there was evidence of an association between paranoid schizophrenia and HLA A9, while the hebephrenic subtype showed a less consistent association with HLA A1 (McGuffin *et al*, 1981). There have now been a total of nine published studies which provide data on an A9-paranoid schizophrenia association (reviewed by McGuffin & Sturt, 1986). Seven of these are consistent with the presence of an association and when the data are pooled it seems highly unlikely that the association has arisen by chance ($\chi^2 = 19.378$, calculated by Woolf's (1955) method, P corrected for number of comparisons = 0.0003). There are, however, a number of difficulties. First, it is not clear whether the diagnosis of a paranoid subtype is comparable in the different centres. Second, A9 is a composite antigen consisting of two subspecificities, AW23 and AW24 (Festenstein & Demant, 1978), and it is uncertain which of these is more important in the paranoid schizophrenia association. Third, and perhaps most importantly, despite its high statistical significance the strength of the association is low. The estimated relative risk of developing paranoid schizophrenia for an A9 positive individual compared with an A9 negative

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individual is 1.6. If we assume, as we have done earlier, a liability/threshold model for the transmission of schizophrenia, then using the method given by Edwards (1965) we calculate that the contribution of the HLA locus to variation in liability to paranoid schizophrenia is only about 1.1%. It therefore appears that the HLA studies may indicate a minor susceptibility locus rather than an important major gene effect in paranoid schizophrenia. The results would therefore require only some slight modification of our earlier speculations that the separation between paranoid and other types of schizophrenia is entirely quantitative and based purely on different thresholds on a liability continuum. Instead we would have to allow that there may also be overlapping sets of polygenes each of which modify the clinical picture in subtly different ways.

By contrast with the association studies, linkage studies which seek to detect a marker gene in close proximity to a major disease gene have been predominantly negative with respect to HLA. Turner (1979) reported that there was suggestive, but inconclusive, evidence of linkage between HLA and 'schizotaxia' in 'typical' families multiply affected by schizophrenia but not in 'atypical' families in which multiple family members were affected not just by schizophrenia but by other conditions such as affective disorder. McGuffin *et al* (1983) failed to replicate this finding and subsequent investigations (Chadda *et al*, 1986; Goldin *et al*, 1987; Andrews *et al*, 1987) are also negative.

So far, there are no published results of studies of schizophrenia and the new genetic markers of recombinant DNA technology, so called restriction fragment length polymorphisms (Botstein *et al*, 1980). But there is considerable optimism about the future usefulness of such markers in detecting major gene effects and resolving problems of heterogeneity in schizophrenia and other common diseases (White *et al*, 1985). Unfortunately the statistical analysis of linkage studies involving conditions with complex and non-Mendelian patterns of inheritance, presents formidable problems which will need to be solved before the 'new genetics' can yield tangible benefits for schizophrenia research (Sturt & McGuffin, 1985).

Conclusions

Although Eugen Bleuler is often regarded as the original instigator of the search for separate subforms of schizophrenia, his son Manfred Bleuler (1978) has more recently concluded that there is little compelling evidence of their existence. This accords well with our own assessment that despite considerable efforts to define subtypes and despite the conviction of many research workers that natural lines of cleavage might exist, no convincing split extending back to a genotypic level has yet been demonstrated in schizophrenia. Time honoured clinical separations of schizophrenia into paranoid and hebephrenic or other non-paranoid subtypes produce a tendency toward homotypia in family and twin studies as do some more recently derived statistically based categories (Farmer *et al*, 1984). However, neither approach produces a clear qualitative separation and the available data can best be explained using liability threshold models in which the subtypes of disorders lie on the same continuum. Although theoretically attractive, subtypologies based on the presence or absence of negative symptoms or on a Crow type I–type II pattern of symptoms do not appear to provide separate, genetically distinct subentities. Similarly a separation of schizophrenia into a distinct familial and sporadic categories is difficult to justify on the basis of current evidence. Rather than providing a means of 'carving nature at the joints', the systems of classifying subtypes which are so far available appear to offer different ways of slicing up the salami. Undoubtedly the salami has more genetic content at one end than at the other, but as yet there is no convincing evidence that we are dealing with two or more completely different varieties of sausage.

Nearly all of the debate on the unity or diversity of schizophrenia has so far been based upon recurring clusters of clinical features. We have been dealing with what Gottesman & Shields (1972) have called 'exophenotypes' which are distantly removed from what must be occurring at a genotypic level. Future prospects for a better understanding of subtle morphological or pathophysiological change which may occur in the living brain of the schizophrenic have been greatly enhanced by recent developments in brain imaging (Buchsbaum *et al*, 1982; Herold & Frackowiak, 1986) and refinements of regional blood flow techniques (Weinberger *et al*, 1986). However, for the present perhaps the most consistent pointer toward a qualitative distinction between subtypes of schizophrenia has so far come from genetic marker studies involving the HLA system. The size of the HLA-paranoid schizophrenia association is small and would be quite in keeping with a multifactorial view of the aetiology of the condition. However, this represents a starting point for future genetic marker studies and signals the passage of psychiatric genetics into a new phase in which the molecular biological aspects of mental disorders must inevitably merit more detailed attention.

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