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The Continuum of Psychosis and its Implication for the Structure of the Gene

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Three observations challenge Kraepelin's binary view of the functional psychoses: a bimodal distribution of the clinical features of manic-depressive illness and schizophrenia has not been demonstrated; affective illness appears to predispose to schizophrenia in later generations; and 'schizoaffective' illnesses cannot be separated in family studies from either of the prototypical psychoses. The alternative concept is that psychosis is a continuum extending from unipolar, through bipolar affective illness and schizoaffective psychosis, to typical schizophrenia, with increasing degrees of defect. According to this concept the genes predisposing to psychosis have a degree of stability that ensures that the form of the psychosis tends to remain the same within families, but there is also the possibility of change, implying that the genetic mechanisms themselves are variable. It is proposed that quantal changes in the 'virogene' are due to replications within the genome (e.g. the generation of tandem repeats of the element or a component of it); that such replications occur at a critical stage (e.g. gametogenesis, fertilisation, very early embryogenesis) in the course of reproduction; and that the 'season of birth effect' reflects the operation of the mechanism responsible for these replications.

Contemporary classifications of psychiatric disease owe much to Kraepelin (1899). At the end of the last century he distinguished the organic from the functional psychoses[1] and, in the latter category, separated manic-depressive insanity from dementia praecox (schizophrenia). The separation was achieved on the basis of outcome—an episodic course with recovery from individual episodes was regarded as characteristic of manic-depressive illness, while in dementia praecox an element of persistence and even progression was to be expected. Although exceptions are recognised, this generalisation on outcome has survived relatively unchallenged.

Kraepelin's 'binary' view has dominated subsequent work to the extent that the entities of schizophrenia and manic-depressive illness are widely regarded as separate diseases, each with a different genetic background, treatment and outcome (Gershon & Rieder, 1980; Loranger, 1981). The earlier view (Guislain, 1833; Neumann, 1859; Griesinger, 1861) that there is a unity in the psychoses (the 'einheit-psychose') has yielded to common observation that typical cases of manic-depressive illness and schizophrenia have distinct psychopathological features, usually follow their predicted courses, and are associated with an incidence of similar illnesses in first degree relatives.

This paper presents an alternative to Kraepelin's binary concept. Doubts about the binary hypothesis arise firstly from the failure of Kendell and co-workers (Kendell & Gourlay, 1970; Kendell & Brockington, 1980) to achieve a bimodal separation of the two conditions on the basis of symptoms or outcome. Secondly, the similarity of season of birth and season of onset effects suggests that the psychoses share aetiological determinants. Thirdly, in family studies two findings indicate that the conditions are more closely related genetically than is generally believed: several investigations have shown an excess of children with schizophrenia among the offspring of parents with affective disorder, and studies of 'schizoaffective psychosis' have failed to separate this entity from either affective disorder or schizophrenia.

The alternative concept is that there is a continuum of psychosis extending from pure affective disorder to schizophrenia with the defect state. The existence of such a continuum would imply that the genetic mechanisms postulated to underlie it are subject to more rapid change than is associated with most human genes.

Limitations of the binary concept

A persistent problem for the binary view has been the undoubted occurrence of psychoses with both manic-

depressive and schizophrenic symptoms. Kasanin (1933) introduced the concept of 'schizoaffective psychosis' and initiated discussion as to whether such illnesses are variants of one or other of the prototypes, or constitute a 'third psychosis'.

It is generally assumed that 'true' schizoaffective psychoses, which cannot be placed in either category, are relatively rare, and that the majority of psychotic illnesses can be classified as either affective or schizophrenic. It would thus be expected that a discriminant function based on the characteristic features would separate the two conditions with relatively few intermediate cases. In testing this prediction on data from the US/UK Diagnostic Project, collected using the Present State Examination and a semi-structured history schedule, Kendell & Gourlay (1970) on the contrary found a distribution with a maximum of cases at the mid-point between the two typical pictures (Fig. 1). A discriminant function which

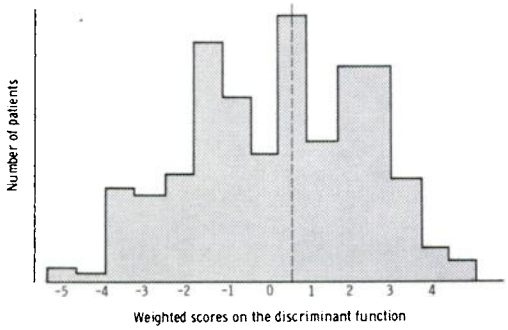

FIG. 1 The distribution of the weighted scores of 146 patients with schizophrenia and 146 patients with affective disorder from the US-UK study on the discriminant function derived by Kendell & Gourlay to maximise separation of the conditions (redrawn with permission from Kendell & Gourlay, 1970)

included all those items which best distinguished patients with a project diagnosis of affective disorder from those with a diagnosis of schizophrenia did not separate two groups at either end of the distribution.

In further sample ($n=217$) Kendell & Gourlay again failed to demonstrate bimodality—this time the distribution on the discriminant function was uni-modal rather than tri-modal. Such findings cast doubt on the common clinical assumption that most cases of psychosis can be relatively easily classified as either affective or schizophrenic.

Returning to the attack, Kendell & Brockington (1980) developed a method for ascertaining a non-linear relationship between symptomatology and outcome, but were unable to demonstrate such relationships in samples of 127 unselected psychotic and 105 schizoaffective patients. They wrote: "no firm conclusions can be drawn about the relationship between schizophrenic and affective psychoses, though it has to be noted that yet another attempt to demonstrate discontinuity between them has failed."

The diagnostic boundaries of schizophrenia have for long been debated. Nuclear symptoms (e.g. thoughts experienced as alien or as auditory hallucinations) were advanced by Schneider (1957) as pathognomonic, but they define a restricted range of illnesses, and are not directly related to poor outcome (Bland & Orn, 1980). An alternative strategy adopted in recent research criteria (e.g. the DSM–III criteria (American Psychiatric Association, 1980), and the earlier criteria of Feighner *et al*, 1972) is to include duration as a defining feature. Such criteria are successful in predicting outcome. Outcome for the schizoaffective psychoses, whether studied before (Hunt & Appel, 1936; Clark & Mallett, 1963) or after (Croughan *et al*, 1974; Brockington *et al*, 1980) the introduction of operational criteria, is found to be intermediate between schizophrenia and affective disorder. Thus, although bimodality of outcome has been claimed in one study (Cloninger *et al*, 1985), experience with schizoaffective illness does not appear to support it.

The two prototypical psychoses share some salient features. Both show a tendency to recur, more striking in the case of manic-depressive psychosis but present also in schizophrenia. Onset before puberty is rare in either case, but the disease can occur at any point in adult life, the mean onset of schizophrenia being earlier (by a decade or more) than affective illness. The lifetime prevalence of both conditions approaches 1%. In neither case have characteristic histopathological changes in the brain been established, although recent neuroradiological (Johnstone *et al*, 1976) and post-mortem studies (Brown *et al*, 1986) suggest structural changes (e.g. cerebral ventricular enlargement) which are more marked in schizophrenia. Seasonality of onset and of date of birth have been widely discussed as a lead to the aetiology of schizophrenia; such illnesses are more likely (by about 5–10%) to have an onset in the early summer months than at other times of the year, and patients with these illnesses are more likely to have been born in the winter months (Dalen, 1975). These trends follow the seasons in the north and south hemispheres. Similar effects have been found for manic-depressive illness (Hare & Walter, 1978) (Fig. 2).

Two explanations of the similarity of these findings in affective and schizophrenic psychoses suggest

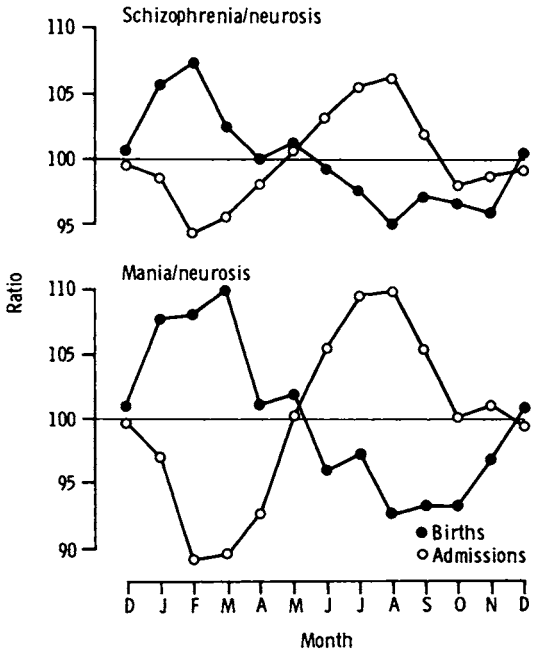

FIG. 2 Monthly births and admissions for schizophrenia and mania expressed as a percentage of the number expected on the basis of overall numbers of births and admissions for neurosis: points represent three-monthly moving averages (redrawn with permission from Hare and Walter, 1978)

themselves: that a statistical artefact has an influence on both sets of data, or that the conditions share a fundamental relationship to the seasons. Such artefacts as have been suggested have been effectively dismissed (Watson *et al*, 1982; Pulver *et al*, 1983), and therefore the second possibility must be seriously entertained.

The prophylactic value of medication is established in both conditions—lithium in preventing relapse in affective illness (Davis, 1976), and neuroleptic medication in schizophrenia (Davis, 1975). Although such drug specificity suggests differences in the underlying disease processes, some schizophrenic illnesses respond to lithium (Biederman *et al*, 1979; Delva & Letemendia, 1986), and in addition to their efficacy in mania, neuroleptics may be of value in depression (Hollister *et al*, 1967). Thus no unequivocal demarcation of the functional psychoses can be made on the basis of symptoms, outcome or response to treatment, and the seasonality effects suggest an underlying aetiological unity.

Are schizophrenia and affective psychosis genetically related?

It is widely held that the genetic factors which predispose to the two typical psychoses are unrelated. Thus according to Gershon & Rieder (1980), "evidence from twin and family studies suggests that bipolar manic depressive illness and chronic schizophrenia are distinct entities", and according to Reich *et al* (1982) "the genetic diathesis for affective disorders is independent of that for other psychiatric disorders". Several findings suggest that such conclusions are too dogmatic. Rather, the two conditions appear to be related in a way which reveals something about the genetic mechanisms. Specifically, affective illness in one generation may predispose to schizophrenia in the next.

In a survey of the risk of other psychiatric illness in first-degree relatives of patients with affective disorder, Rosenthal (1970) noted an excess of schizophrenia in children (a mean of 2.3% in 5 studies),

TABLE I
Psychotic offspring of psychotic parents classified by diagnosis

Offspring	*Parents*	
Penrose (1968)	*Affective disorder*	*Schizophrenia*
Affective disorder	232	34
Schizophrenia	205	150
Powell et al (1973)	*Manic-depressive psychosis*	*Schizophrenia*
Manic-depressive psychosis	10	0
Schizophrenia	15	9

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while the risk in parents and siblings remained within the 0.8% lifetime prevalence for the general population. He asked: "From the genetic point of view, why should schizophrenia have occurred at all in these families?"

Two studies have examined parent–child pairs in which both members suffered from psychosis (Table I). Penrose (1968) identified 621 such pairs in a series of 5456 pairs of relatives with psychiatric disease collected over a period of 18 years in the Ontario Mental Hospitals. Among the ill children of schizophrenic parents a diagnosis of schizophrenia preponderated over affective disorder in a ratio of almost 5:1. Among the children of affectively ill parents the ratio was a little less than 1; schizophrenia was almost as common as affective disorder. In a similar study on the Aberdeen case register Powell *et al* (1973) found schizophrenia in the children of schizophrenic parents and affective illness among the children of parents with affective disorder as expected. However, among the latter they found that for 10 cases of affective disorder, 15 cases of schizophrenia were also present.

These findings suggest an excess of schizophrenia among the children of affectively ill parents[2]; this seems unlikely to be due to a secular trend toward diagnosing more schizophrenia, or to selective factors (e.g. hospital admission) leading to over-inclusion of patients with schizophrenia, as the two samples were collected 30 years apart on either side of the Atlantic, one from in-patient records and the other from a case contact register.

In a series of 25 children of two manic-depressive parents, Schulz (1940) reported that 7 suffered from affective illness but 3 suffered from schizophrenia. In applying more restrictive diagnostic criteria to a larger literature, Elsasser (1952) found that of 169 children of two parents with manic-depressive or atypical psychoses (i.e. with schizophrenia excluded), 18 suffered from definite affective illness and 6 from definite schizophrenia.

Pollock & Malzberg (1940) collected family histories of psychosis over three generations. In relatives in preceding generations (parents, grandparents, uncles and aunts) of patients with schizophrenia they found an excess of affective illness: 15 cases of affective illness compared with 11 of schizophrenia (Table II).

Slater (1953) reported similar findings. In his study of twins he recorded psychiatric illness in other relatives, and found the ratio of affective disorder to schizophrenia (4:3) particularly high in the parents of patients with schizophrenia. The corresponding ratio (3:5) for siblings similarly showed more affective disorder than would conventionally be expected (Table II). No excess of schizophrenia was found in the parents or siblings of patients with affective disorder.

TABLE II

Psychotic illness in the preceding generations and siblings of patients with affective disorder or schizophrenia

Relative group	*Proband diagnosis*	
	Affective disorder	*Schizophrenia*
Pollock & Malzberg (1940)	($n=155$)	($n=175$)
Preceding generations (parents, uncles, aunts, grandparents)		
Manic-depressive psychosis	7	15
Schizophrenia	3	11
Siblings		
Manic-depressive psychosis	11	2
Schizophrenia	3	8
Slater (1953)	($n=38$)	($n=156$)
Parents		
Affective disorder	9	16
Schizophrenia	0	12
Siblings		
Affective disorder	12	15
Schizophrenia	1	26

TABLE III
Risk of psychosis in the first-degree relatives of probands with schizoaffective illness: percentages of relatives affected

Type of psychosis	*Angst* et al, *1979* (*n*=150)	*Tsuang* et al, *1977* (*n*=52)	*Baron* et al, *1982*[1] (*n*=50)	
			SA-A	*SA-S*
Schizophrenia	5.26	0.9	0	4.1
Schizoaffective psychosis	2.97	—	3.2	1.4
Affective psychosis	6.70	11.8	28.1	10.9

1. Schizoaffective illness was subdivided into mainly affective (SA-A) and mainly schizophrenic (SA-S) subtypes

In an earlier study of manic-depressive illness (Slater, 1936) "a surprising feature had been the number of schizophrenics among the children ... In 10 of the 15 cases where manic-depressive subjects had been found by Dr Slater to have schizophrenic children he had been unable to find schizophrenia in other members of the patient's family or that of the husband or wife".

Each of these observations, therefore, is consistent with a one-way movement between generations from affective disorder to schizophrenia. On the basis of his own family studies Myerson (1925) summarised what he believed to be the inheritance of mental disease: "that the manic-melancholic diseases are in the main followed by manic-melancholic diseases, but in a certain number, especially of doubtful cases by dementia praecox ... that the manic-depressive states of involution trend toward manic-depressive and dementia praecox, especially the latter ... that dementia praecox in an ancestor trends toward dementia praecox in the descendants with a certain scattering incidence of imbecility."

Such a notion is an echo of the concept of the degeneration psychosis as formulated by Morel (1860) and Magnan (1893). As a genetic theory it is unorthodox, but on the accumulated literature looked at from an intergenerational standpoint it appears it cannot be easily dismissed.

The genetics of schizoaffective disorder

On account of the historical origins of the concept of schizoaffective psychosis and its pivotal position in nosology, particular interest attaches to the genetics involved.

In the largest study to date, Angst *et al* (1979) found the risk of schizophrenia and affective disorder to be approximately equal in first degree relatives of schizoaffective probands, and that of schizoaffective illness to be appreciably less than that of either of the prototypical psychoses (Table III). Two other surveys (Tsuang *et al*, 1977; Baron *et al*, 1982) found schizoaffective disorder to be more closely related to affective illness than to schizophrenia. Each group of researchers inferred that schizoaffective illnesses are not genetically separate from the major (particularly affective) psychoses. The conclusion that schizoaffective illness is not a genetic entity was also reached by Tsuang (1979) in a study of pairs of siblings with psychosis. When diagnoses were blindly allocated to the categories of schizophrenia, affective disorder, and schizoaffective disorder, a deficit of schizoaffective × schizoaffective pairs was observed relative to the number of such diagnoses in the sample. Eight schizoaffective × affective, five schizoaffective × schizophrenic, and two schizophrenic × affective pairs were present in a sample of 35 pairs.

The relationship of schizoaffective illness to the affective disorders is illuminated by Gershon *et al*'s (1982) study with modified Research Diagnostic Criteria of 1254 relatives of patients with major affective disorder: "These data were compatible with the different affective disorders representing thresholds on a continuum of underlying multifactorial vulnerability. In this model schizoaffective illness represents greatest vulnerability, followed by bipolar ... then unipolar (affective) illness". These authors thus espouse a continuum concept which extends up to schizoaffective illness but excludes schizophrenia.[3]

If schizoaffective disorder does not breed true and has a relationship (as suggested by Tsuang *et al* (1977), Baron *et al* (1982) and Gershon *et al* (1982)) to affective disorder, the question arises whether an excess of schizoaffective illness (or affective disorder) is seen amongst first degree relatives of patients with schizophrenia when schizophrenia is narrowly defined as in recent operational criteria. Kendler *et al*

TABLE IV

Morbid risk of schizophrenia, affective disorder, schizoaffective disorder and atypical psychosis (determined by DSM–III criteria) in blindly assessed first degree relatives of patients with schizophrenia and surgical controls (from Kendler et al, *1985)*

Diagnosis	*Relatives affected: %*		*P*
	Schizophrenics (n=332)	*Controls (n=318)*	
Schizophrenia	3.7	0.2	7.9×10^{-8}
Schizoaffective disorder	1.4	0.1	0.008
Atypical psychosis	2.5	0.3	0.0006
Affective disorder			
Unipolar	6.0	7.6	NS
Bipolar	1.2	0.3	NS

(1985) reanalysed a consecutive series of 510 patients with a chart diagnosis of schizophrenia from the Iowa Hospitals with the DSM-III criteria, and compared rates of illness in the relatives of 332 patients with a DSM-III diagnosis of schizophrenia with those in relatives of 318 surgical controls. In their analysis of personal interview or hospital records these authors found that while the risk of affective disorder was not significantly increased, the risk of schizoaffective disorder and atypical psychosis was (Table IV). Even with a restrictive definition of schizophrenia, therefore, no 'genetically pure' syndrome is isolated, and a relationship with the schizoaffective spectrum remains.[4]

Thus it seems that schizoaffective illness occurs in the relatives of patients with both schizophrenia and affective disorder even when these illnesses are restrictively defined. Unless schizoaffective disorder can be partitioned into schizophrenic and affective types of illness (and since the concept originated in the failure of such an enterprise, this seems unlikely), parsimony requires the conclusion that schizoaffective disorder is but the bridge between affective disorders and schizophrenia.[5] The psychoses constitute a genetic continuum rather than two unrelated diatheses (Crow & Cooper, 1986).

The genetics of a continuum

However, there is also a degree of stability of clinical picture within families; without this, the Kraepelinian dichotomy could hardly have survived.[6] Within families (perhaps particularly within generations) the form of the psychosis tends to breed true. Such a trend is accentuated when (as often in genetic studies) cases which do not fit the two classical pictures are excluded from consideration. A more faithful representation is obtained when the series of cases is unselected and intermediate diagnoses of probands and relatives are allowed. Thus in his series of consecutive admissions with psychosis Ødegaard (1972) included schizophrenic psychoses of three grades of defect, and the categories of schizophrenia without defect, reactive psychosis and atypical affective psychosis cover most of what would be described as schizoaffective illness in other classifications. The incidence and type of illness in relatives (Fig. 3) is

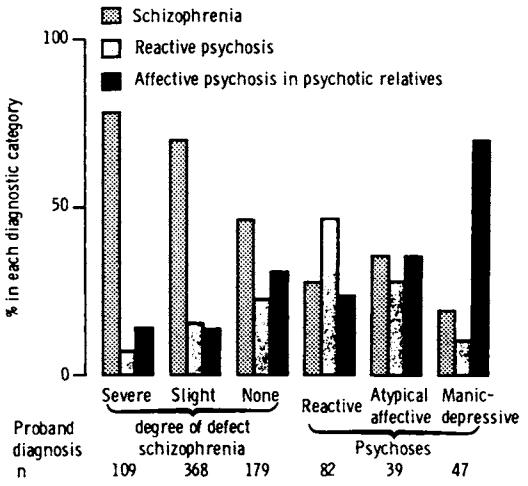

FIG. 3 Relative risks of psychiatric disorder, classified from case histories, in the first and second degree relatives of a consecutive series of admissions of patients with psychosis (data taken from Ødegaard, 1972)

compatible with the concept of a genetic continuum along which conditions are distributed with increasing severity from typical manic-depressive psychosis to schizophrenia with severe defect. Within this continuum particular forms of illness are genetically related to those nearby. The inter-relatedness of the two ends of the continuum, however, is limited.

The hypothesis of a continuum of psychosis is a development of the concept of the 'unitary psychosis' espoused in the last century by Guislain, Neumann, and Griesinger and more recently by others (Llopis, 1954; Menninger *et al*, 1958; Karlsson, 1974; Rennert, 1982; Flor-Henry, 1983). The refinement is that the psychoses are represented on a continuum (Fig. 4) from pure affective illness to deteriorating schizophrenia.[7]

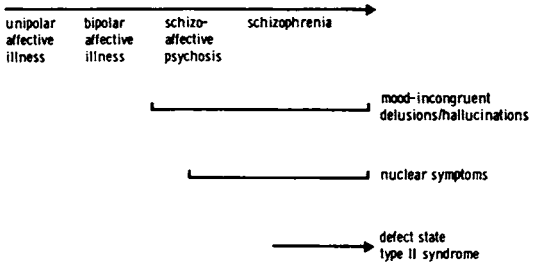

FIG. 4 The continuum concept. Brackets indicate the range over which mood-incongruent psychotic phenomena and nuclear symptoms may occur

That movement along this continuum occurs is documented by Ødegaard's study and the studies on schizoaffective disorder; that such movements take place in the course of reproduction is suggested by the systematic trend in the intergenerational studies. For the children of parents with one type of psychosis the risk of an illness of greater severity is increased. These phenomena cast some light on the nature of the underlying genetic mechanisms. They intimate that in the psychoses we observe the manifestations of quantum changes in a variable gene. One possibility is that at some critical stage of the reproductive process (e.g. meiosis, fertilisation) tandem repeats of a mobile genetic element (or of some component of that element) are generated.

The nature of the psychotic continuum

The persistence of the psychoses in spite of a fertility disadvantage, well documented in the case of schizophrenia but possibly also associated with manic-depressive psychosis (Stevens, 1969), raises the question of whether the gene confers advantages on relatives of patients with psychotic illness. In Iceland, Karlsson (1984) noted that such relatives were over-represented, as recorded in the Icelandic *Who's Who*, in public life and the professions. Karlsson (1978) also drew attention to the frequency of a history of mental illness in compendia of those distinguished in literature, mathematics and philosophy. Others (Andreasen & Powers, 1975; Jamison, 1986) have documented the prevalence of significant affective disturbance in writers and poets. The nature of the relationship between the two typical psychoses and achievement is illuminated by Noreik & Ødegaard's (1966) study of Norwegians with a background of higher education. Among high school graduates they found admissions increased with respect to general population expectation for a diagnosis of manic-depressive psychosis in both sexes and for schizophrenia in females. In studying admission rates in relation to occupation, they found that the group comprising the liberal professions, teaching and higher officials had first admission rates for manic-depressive psychosis twice those of the general population (151, compared with 73), but admission rates for schizophrenia were reduced (305, compared with 357 for the general population).

Such associations suggest that the gene has beneficial as well as adverse consequences, and that the balance between them is seen only when the psychoses are considered together. However, it remains to be demonstrated that these effects are related to gene survival. There appear to be two possibilities—that the gene or a component element promotes fertility in (as yet unidentified) relatives of psychotic individuals, or that the element is able to replicate between haploid genomes, as suggested for mobile genetic elements by Hickey (1982), and thus to persist against a fertility disadvantage.

A clue to the nature and functional significance of the variable underlying psychosis is Flor-Henry's (1969) observation that the psychoses associated with temporal lobe epilepsy are commonly schizophrenic when the lesion is on the left side and affective when it is on the right side of the brain. Recent (and some earlier) studies of brain structure support the view that schizophrenia itself is a disease with a degree of selectivity for the left hemisphere (Crow, 1986). Such observations raise the possibility that the genetic determinants of brain lateralisation and psychosis are related.

Asymmetries in the human brain are now well established (Galaburda *et al*, 1978): structures in the superior temporal lobe, including the auditory

assciation cortex, are better developed on the left than on the right side of the brain (at least in right-handed individuals). These asymmetries are a relatively recent evolutionary development being shared by man with the gorilla (Groves & Humphrey, 1973) the orang utan (Le May & Geschwind, 1975) and the chimpanzee, but not the rhesus monkey (Yeni-Komshian & Benson, 1976). Presumably they are related to the cerebral mechanisms of communication and speech. In man the asymmetries are associated with cerebral dominance and handedness, a genetically determined attribute whose persistence as a polymorphism is as yet unexplained.

Since differential brain growth occurs, one must suppose that the genes involved code for one or more growth factors. These genes, e.g. the 'cerebral dominance gene' or 'right shift factor' (Annett, 1978, 1985), could be the location of the genetic changes underlying psychotic illness. One possibility is that a viral gene (e.g. a retrovirus or other type of mobile genetic element or 'transposon') is integrated at this site (Crow, 1984). If the presence of such a gene were associated with increased growth but the gene was sometimes expressed as viral particles this could explain the postulated benefits as well as the disruptive cerebral effects, and possibly the episodic nature of the illness.

Conclusions

It is concluded that the affective psychoses and schizophrenia are related to each other on a continuum, and that this continuum has a genetic basis. This concept is founded in the failure of Kendell & Gourlay's attempts to separate the conditions by symptomatology and in the similarities in season of birth and season of onset effects for the two prototype disorders. It is sustained by observations that schizoaffective psychoses (states defined as intermediate between the major psychoses) do not breed true and cannot be excluded from the relatives of patients with affective disorder or schizophrenia when these are defined by stringent criteria. Therefore, by an inductive (in a mathematical sense) argument as well as from the evidence of studies of symptomatology and outcome, there is a case for a continuum of psychosis which increases in severity from unipolar through bipolar affective disorder to schizoaffective disorders and schizophrenia with increasing degrees of defect. The existence of such a continuum and the excess of individuals with schizophrenia among the descendants of patients with affective disorder provide clues to the nature of the genetic mechanisms. The genes responsible appear to be subject to quantum changes. Perhaps these genes survive because they are closely related to growth factors responsible for the development of cerebral asymmetry and the mechanisms of dominance. Such relatively late evolutionary developments may be associated with a high degree of genetic variation.

Notes

1. According to G. E. Berrios (in preparation), the concept of functional psychosis is unlikely to have originated with Kraepelin, although it was adopted by him. It may have been introduced by E. Mendel.

2. Cammer (1970) also commented on the incidence of schizophrenia in the children of manic-depressive parents. In a personal case record study he judged that 148 (26.6%) of 533 children of 273 manic-depressive parents were "schizophrenes", but the diagnostic criteria adopted are broad and the age structure and hospitalisation histories of this series were not given.

3. It is of interest that in Gershon *et al*'s (1982) investigation there was an excess ($P<0.001$) of schizophrenia among the relatives of patients with schizoaffective illnesses in comparison with those having other types of affective illness. Also of note with respect to inter-generational effects is the finding that the risk of schizoaffective illness in the siblings of the generation succeeding the proband is increased (at 3.9% age-corrected lifetime risk) in comparison with siblings of the proband (0.8%) and siblings of members of the generation preceding the proband (0%).

4. It is also of interest that an earlier study (Tsuang *et al*, 1980) of the Iowa series, which did not allow schizoaffective diagnoses, supported the distinction between schizophrenia and affective disorder "although the distinction between schizophrenia and mania was not clear-cut". Subtyping of paranoid and non-paranoid schizophrenia and of unipolar and bipolar affective disorder on the basis of familial associations was not supported. These conclusions do not appear to rule out a continuum concept.

5. A number of studies have related outcome in schizophrenia to incidence of atypical or affective psychoses in relatives. Thus Kant (1942) studied family histories of 50 deteriorated and 50 recovered schizophrenic patients and found that while overall rates of psychosis were similar in the two groups, the ratio of schizophrenia to affective disorder was 5:1 in the former and 1:5 in the latter. However, he notes that "none of the manic-depressive patients among the relatives of the recovered group actually belong to the manic-depressive nucleus . . . there are several whose clinical pictures remind one strongly of the corresponding atypical types in the recovered schizophrenic group". With a parallel strategy, Kendler & Hays (1983) studied patients with schizophrenia diagnosed by DSM-III criteria, and identified a group of 18 with a first-degree relative with unipolar affective disorder and 10 with a relative with bipolar affective disorder, whom they compared with a group of 98 with no affective disorder in first degree relatives. These authors commented on their own and some other authors' apparently high rates of affective disorder in relatives as "probably representative of most families of schizophrenics". Patients with a family history of affective disorder were more likely to have suffered from affective symptoms on follow-up. Kendler & Hays concluded that "even when DSM-III criteria are met, hesitation is indicated in diagnosing schizophrenia in patients with a first degree relative with bipolar illness". Similarly, Pope & Lipinski (1978) review 15 studies of "good prognosis", "remitting", and "recovered" schizophrenia and "atypical", "schizophreniform" and "schizoaffective" psychoses and draw attention to the high frequencies of affective illness in the relatives. They warn that "over-reliance on (clinical) symptoms alone results in over-diagnosis of schizophrenia and under-diagnosis

of affective disorder, particularly mania. This compromises both clinical treatment and research".

Underlying the views of Kendler & Hays and Pope & Lipinski is the conviction that the binary concept is correct, but that the location of the borderline has strayed from its position of Kraepelinian rectitude; if this borderline were replaced, symptoms and outcome would separate in the prescribed bimodal manner. The work of Kendell & Gourlay (1970) and Kendell and Brockington (1980) gives no support to this notion. Moreover, in the recent literature the border has moved far in one direction and then far in the other without finding a satisfactory resting place. It is clear from the work of Kendler & Hays (1983) and Kendler *et al* (1985) that the DSM–III criteria do not locate it. It has to be considered that no such natural resting place exists.

6. A recent independent challenge to the Kraepelinian viewpoint is the suggestion that the clinical picture in the individual patient is less constant than is often thought. Thus Sheldrick (1975) and Sheldrick *et al* (1977) draw attention to a group of patients who present with apparently typical schizophrenic illnesses but later suffer from episodes of illness which are affective in form. Conversely, Kendler & Tsuang (1982) report a pair of monozygotic twins, each of whom progressed from typical affective illness to 'process' schizophrenia. They suggest that the progression is genetically determined. Most unexpected, from a Kraepelinian and a genetic viewpoint, is the report of McGuffin *et al* (1982) of identical triplets discordant for psychosis according to binary typology. Each of these findings appears to be exceptional (although the precise frequency of such exceptions is of considerable interest), as can be seen from the findings of the major studies (e.g. Tsuang *et al*, 1980; Gershon *et al*, 1982; Kendler *et al*, 1985), which document the relative stability of clinical picture within families.

7. Ødegaard's (1963, 1972) conception of a "multifactorial" genetic background was based on observations of overlap in family studies in series of consecutive admissions. The notion was particularly well developed in the 1972 paper, in which the range of diagnosis in the proband was extended (Fig. 3). A 'spectrum' concept of the psychoses was also formulated by Beck (1972), without reference to genetic studies. Beck considered that two variables were involved—a schizophrenic variable linked to a poor prognosis, and an affective variable linked to a good prognosis.

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