British Journal of Psychiatry (1988), **153** (suppl. 3), 16–25

Population and Family Studies in Depression and Mania

J. MENDLEWICZ

Recent progress in molecular genetics and neurobiology has attracted much attention and provided a new insight into the nature–nurture controversy in respect of the aetiology of psychiatric disorders. Affective illness, including the various subtypes of depressive and manic syndromes, has been the subject of a considerable amount of research on the relative importance of hereditary and environmental factors. This paper provides a critical review of the most relevant literature on the genetics of depression and mania.

Prevalence

Leonhard (1959) and the Berlin School first proposed a discrimination between bipolar (manic–depressive) and unipolar (depressive) subtypes in affective disorder: bipolar patients experience both mania and depression, whereas unipolar patients experience depression only. However, most of the epidemiological studies on affective disorders have not made this distinction, and various investigators have used different diagnostic criteria for classifying the affective psychoses, so that it is difficult to assess reliably the prevalence of affective illness in the general population. Several investigations, however, have reported lifetime risks for bipolar (manic–depressive) illness in various geographical areas under specific conditions. The rates published vary from a low of 0.07% (Böök, 1953) to a high of 7.0% (Tomasson, 1938): the unusually low rate corresponds to only two cases of bipolar illness in a population of about 9000 in a province of northern Sweden.

Zerbin-Rüdin (1967), who reviewed most population studies in manic–depressive illness, places the overall rate for this disease at around 1%. This is consistent with, although not identical to, the rates published by Slater (1953) for Great Britain (0.5–0.8%), Sjörgen (1948) for Sweden (0.6–0.8%), and Kallman (1954) for New York State (0.4%). These differences in the prevalence of bipolar illness according to the country investigated could be partially explained by genetic factors, e.g. breeding effects and higher consanguinity rates in isolates in Scandinavia, or differences in ethnic background, though environmental factors may also lead to such differences. Sampling artifacts such as the different sizes of the samples studied, and differences in the ethnic and socioeconomic composition of the populations investigated, may also play a role. Furthermore, some studies are based on admission to mental hospitals, and represent an incidence rate rather than a true prevalence; admissions to private and community facilities are rarely included in these surveys. This represents a serious bias, since we know that population rates for a disease may fluctuate with time, according to admission policy or availability of beds: the lifetime hospital admission risk for all affective disorders for England and Wales in 1964 (Ministry of Health, 1969) was 2.4% for males and 5.8% for females – almost a 50% rise for both sexes when compared with 1954, but apparently high rates in certain areas may be true only under special demographic conditions. In addition to differences in sampling, investigators utilise different statistical procedures and even more important, various diagnostic criteria: American psychiatrists used to diagnose schizophrenia more frequently and underdiagnose manic–depressive illness, compared with their British and Western European colleagues, who were prone to diagnose affective illness more often (Cooper *et al*, 1972), though these differences are now much reduced.

Nevertheless, one may conclude from the more reliable lifetime risk studies that 1% would be a conservative rate for the prevalence of bipolar manic–depressive illness in the general population (Ministry of Health, 1969). If one were also to include milder forms of bipolar illness, where a considerable number of subjects are being treated as out-patients, the general prevalence may be as high as 10%.

Most studies have reported an appreciable difference between the sexes in the distribution of bipolar illness (Helgasson, 1964): the sex ratio generally accepted is two females to one male, but interpretation of this excess of females is still controversial. It is conceivable that for cultural reasons, women are more likely to be admitted to hospital for manic–depressive illness than are men, but if this were true, one would also expect to find the same phenomenon for schizophrenia – something that remains to be proved. Another possible explanation, though, is the fact that male suicides outnumber female by a ratio of about two to one (Rüdin, 1923), leaving more females alive than males in the bipolar population. Finally, one could also invoke the hypothesis of

TABLE I
Concordance rates for manic-depressive illness in twins

Study	Concordance rate: % MZ	DZ
Rosanoff *et al* (1934)	69.6	16.4
Kallmann (1954)	92.6	23.6
Da Fonseca (1959)	71.4	38.5
Harvald & Hauge (1965)	50.0	2.6
Kringlen (1967)	33.3	0.0
Bertelsen (1977)	58.0	17.0
Torgersen (1986)	75.0	0.0

sex-limited factors; e.g. hormonal (Zerbin-Rüden, 1967) or sex-linked genetic factors, increasing the expressivity of bipolar illness in females predisposed to this disorder.

Twin studies

The twin method allows comparison of concordance rates for a trait between sets of monozygotic (MZ) and dizygotic (DZ) twins; both types of twins share a similar environment, but they are genetically different. Monozygotic twins behave genetically as identical individuals, whereas DZ twins share only half of their genes and thus behave as sibs. Most twin studies show that the concordance rate for manic-depressive illness in MZ twins is significantly higher than the rate for the disease in DZ twins (Zerbin-Rüdin, 1969), and this observation is taken as evidence in favour of a genetic factor in manic-depressive illness. Table I gives the concordance rate for affective disorder in MZ and DZ twins, according to various investigators who reported on 20 or more pairs (Rosanoff *et al*, 1934; Kallmann, 1954; Da Fonseca, 1959; Harvald & Hauge, 1965; Kringlen, 1967). The concordance rates in MZ twins vary between 50 and 92.5% (mean 69.3%), compared with 0–38.5% in DZ twins (mean 20%); more recent reports from Bertelsen (1977) and from Torgersen (1986) have also produced similar concordance rates, which strongly support the presence of a genetic factor in the aetiology of manic-depressive illness.

Price (1968) reviewed the literature on twins in order to locate pairs of identical twins who had been reared apart since early childhood and who were characterised by at least one of the twins being diagnosed as affectively ill; he was able to find 12 such pairs of MZ twins. Among these pairs, eight were concordant for the disease – an observation suggesting that the predisposition to bipolar illness will usually express itself, regardless of the early environment. However, the complex interaction between hereditary and environmental factors underlying the aetiology of bipolar illness cannot be elucidated by the twin method, nor can it tell us the type of genetic mechanisms that may be involved in the transmission of manic-depressive illness.

Family studies

Most of the early studies on manic-depressive disorder have shown that this illness tends to be familial (Kallmann, 1954): the lifetime risk for the disease in relatives of bipolar probands is significantly higher than the risk in the general population. The risks published by Kallmann were 23.4% for parents of manic-depressive probands, and for sibs 22.7%; in the more distant (second-degree) relatives, the rates usually range from 1 to 4%. It is thus clear that the risks for the illness are decreased as the degree of consanguinity is lowered – as expected if there is a genetic component in the aetiology of this disease. Most of the early family studies were influenced by Kraepelin's classification, so far as nosology is concerned. As a result of this, the aforementioned investigators included among their probands patients suffering from mania and depression (bipolar), without distinguishing between these. Thus, the samples investigated in the various studies are relatively heterogeneous: Leonhard (1959) was one of the first investigators to make a clinical distinction on genetic grounds between bipolar and unipolar forms of affective disorder. The bipolar patients were shown to have a greater genetic loading for affective disorder than the unipolar ones: they also had more relatives with hypomanic temperaments, compared with the unipolar patients, whose relatives had depressive temperaments. It was concluded that bipolar and unipolar disorders may have different genetic aetiologies.

Two recent independent studies have investigated bipolar and unipolar probands separately (Angst, 1966; Perris, 1968): both studies found that the morbidity risks for affective disorders were significantly higher in the relatives of bipolar patients – both bipolar and unipolar illnesses were present in the relatives of bipolar patients, whereas only unipolar illnesses were present in the relatives of unipolar patients. This genetic distinction between unipolar and bipolar illness has also been confirmed by Winokur *et al* (1969): the lifetime risks for affective illness (i.e. bipolar and unipolar) in the first-degree relatives of bipolar patients were 34% for parents and 35% for sibs – similar to the rates we found in the relatives of 134 bipolar probands in New York (Mendlewicz and Rainer, 1974). Table II

TABLE II
Morbidity risks for affective illness in relatives of bipolar manic–depressive patients[1]

	All affective: %	*Bipolar: %*	*Unipolar: %*
Parents	33.7±2.9	12.1±2.0	22.0±2.6
Sibs	39.2±3.0	21.2±2.5	18.6±2.5
Children	59.9±6.0	24.6±5.0	41.3±6.7

1. $n = 134$.
Adapted from Mendlewicz & Rainer (1974).

illustrates the age-corrected risks found in various types of first-degree relatives of bipolar patients: the type of affective disorder found in the relatives of bipolar patients was not restricted to bipolar illness, the risk for unipolar illness being quite significant in these relatives. The overall rates for affective illness are similar in sibs and parents, but sibs are more likely than parents to manifest bipolar illness.

Children of bipolar probands constitute a high-risk group; from a review of all family studies, the risk for manic–depressive illness in the relatives of affected patients can be estimated at somewhere between 15 and 35%, but there is a large proportion of relatives of bipolar probands who exhibit unipolar illness only. When correction has been made for age, diagnosis, and statistical procedures, the morbidity risks for manic–depressive illness in different types of first-degree relatives (parents, sibs, children) are similar – an observation which is consistent with a dominant mode of transmission.

Despite the high prevalence of unipolar depression in the general population, few genetic studies are available on subtypes of unipolar illness. We evaluated morbid risks for depression, alcoholism, and/or sociopathy in the relatives of early-onset (before age 40) and late-onset (after age 40) unipolar patients, in a sample of 106 probands. Table III summarises the results of this study (Mendlewicz & Baron, 1981). Unipolar patients with early-onset disease had a greater familial morbidity for depression, alcoholism, and sociopathy than those with late-onset disease. There was an excess of unipolar depression in female relatives of early-onset unipolars when compared to late-onset probands, regardless of the proband's sex. Alcoholism and sociopathy were also more prevalent in the relatives of early-onset unipolars versus late-onset probands. The morbidity risks showed familial genetic differences between early- and late-onset forms of unipolar illness, and partially confirmed Winokur's concept of two subtypes of unipolar depression.

Adoption studies

Few adoption studies are available in relation to affective disorders. In the study of Cadoret (1978), adopted-away offspring of affectively ill biological parents presented significantly more depressive disorders (mainly unipolar illness) in adulthood than

TABLE III
Morbid risk for unipolar depression in parents and sibs of unipolar probands, according to age of onset

	Number ill	*Number at risk*	*Morbid risk: %*
Early onset			
Mothers	22	68	32.3±5.6
Fathers	4	70	5.7±1.8
Sisters	21	68	30.8±6.1
Brothers	6	42	14.3±5.5
Mothers and sisters	43	130	[1,2]33.0±5.2
Fathers and brothers	10	112	8.9±3.9
Late onset			
Mothers	10	60	16.6±4.8
Fathers	4	59	6.7±2.9
Sisters	10	40	25.0±5.1
Brothers	8	63	12.7±3.2
Mothers and sisters	20	106	18.8±4.1
Fathers and brothers	12	122	9.8±2.2

1. $\chi^2 = 5.28$, d.f. = 1, $P < 0.05$ vs morbid risk in mother and sisters on late onset probands.
2. $\chi^2 = 22.5$, d.f. = 1, $P < 0.001$ vs morbid risk in fathers and brothers of early onset probands.
Adapted from Mendlewicz & Baron (1981).

TABLE IV
Diagnosis of parents for bipolar adoptees and non-adoptees

	Bipolar adoptees (n = 29)				*Bipolar non-adoptees (n = 31)*	
	Adoptive parents		*Biological parents*		*Biological parents*	
	Male	*Female*	*Male*	*Female*	*Male*	*Female*
Bipolar	1	0 (1)[1]	3	1 (4)	2	0 (2)
Unipolar	2	3 (6)	1	11 (12)	3	8 (11)
Schizoaffective	0	0 (0)	0	2 (2)	1	0 (1)
Cyclothymic	0	0 (0)	0	0 (0)	1	1 (2)
Affective spectrum	4	3 (7)[2]	4	14 (18)[2]	7	9 (16)
Percentage	14	10 (12)	14	48 (31)	23	29 (26)
Schizophrenia	0	0 (0)	0	0 (0)	0	1 (1)
Alcoholism	2	0 (2)	2	1 (3)	1	1 (2)
Sociopathy	0	0 (0)	1	1 (2)	0	1 (1)
Other	0	0 (0)	0	0 (0)	0	0 (1)
All psychopathology	6	3 (9)[3]	7	16 (23)[3]	8	12 (20)
Percentage	21	10 (16)	24	55 (40)	26	39 (32)

1. Figures in parentheses are totals.
2. $\chi^2 = 5.10$, $P < 0.025$.
3. $\chi^2 = 7.29$, $P < 0.01$.
Adapted from Mendlewicz & Rainer (1977).

did adoptees whose biological parents were well or had other psychiatric conditions. Mendlewicz & Rainer (1977) investigated parents (biological and adoptive) of bipolar manic-depressive adoptees who had been raised in adoptive families, and parents of two control groups. Comparison of adoptive parents of persons with a psychiatric disorder with the adoptees' biological parents provides a unique opportunity to separate the interacting aetiological roles of heredity and environment respectively. The major finding was that psychopathology in the biological parents is in excess of that found in the adoptive parents of the same manic-depressive offspring (Table IV). If we focus on 'affective spectrum' disorders – namely bipolar affective disease (episodes of mania and depression), unipolar affective disease, depressions without mania, schizoaffective psychosis, and cyclothymic personality – the difference is significant at the level of $P < 0.025$ ($\chi^2 = 5.10$). Previous genetic studies support the inclusion of unipolar and schizoaffective disorders as genetically related to bipolar illness, when they are found in close relatives of bipolar patients (Winokur *et al*, 1969; Mendlewicz & Rainer, 1974); if other forms of psychopathology are included, the difference is highly significant ($\chi^2 = 7.29$, $P < 0.01$). The frequency of non-affective psychopathology was no higher, in the biological parents of bipolar adoptees (9%) than in those of normal adoptees (16%) (Table V), indicating that it is by virtue of the affective disorders that the former differ from the latter (31% compared with 2%).

The degree of psychopathology in the biological parents of manic-depressive adoptees is similar to that of the parents of the non-adopted manic-depressives, while the rate of psychiatric disorder in the adoptive parents of the experimental group is similar to that of the adoptive parents of the normal offspring group. The degree of total psychopathology in the biological parents (of normal offspring) who gave their children for adoption is slightly greater than in adopting parents who brought up those same individuals (Table V). This difference is due to an excess of alcoholism and sociopathy in the former group. Finally, the degree of psychopathology in the parents of polio patients is in the same range as in both groups of adoptive parents (Table V). All these findings support the conclusion that our experimental sets of parents are truly representative of the degree of psychiatric disorder which is present respectively in those parents who bring up, and in those who contribute genetically to manic-depressive individuals.

In the follow-up process of this study, it was also possible to investigate a certain number of both biological and adoptive sibs of the bipolar manic-depressive adoptees (Mendlewicz, 1986). Twelve adoptive sibs, not biologically related to the adoptees (four females, ages 28 to 34, and eight males, ages 29 to 33) – all biological children of the adoptive

TABLE V
Diagnosis of parents for normal adoptees and non-adoptees

	Normal adoptees (n = 24)				*Poliomyelitis (n = 20)*	
	Adoptive parents		*Biological parents*		*Biological parents*	
	Male	*Female*	*Male*	*Female*	*Male*	*Female*
Bipolar	0	0 (0)[1]	0	0 (0)	0	0 (0)
Unipolar	1	2 (3)	1	0 (1)	3	1 (4)
Schizoaffective	0	0 (0)	0	0 (0)	0	0 (0)
Cyclothymic	1	0 (1)	0	0 (0)	0	0 (0)
Affective spectrum	2	2 (4)	1	0 (1)	3	1 (4)
Percentage	10	10 (10)	5	0 (2)	15	5 (10)
Schizophrenia	0	1 (1)	0	0 (0)	0	0 (0)
Alcoholism	0	0 (0)	1	2 (3)	1	0 (1)
Sociopathy	0	0 (0)	2	1 (3)	0	0 (0)
Other	0	0 (0)	0	1 (1)	0	0 (0)
All psychopathology	2	3 (5)	4	4 (8)	4	1 (5)
Percentage	9	14 (11)	18	18 (18)	20	5 (12)

1. Figures in parenthesis are totals.
Adapted from Mendlewicz & Rainer (1977).

parents – were compared with nine biological sibs of the adoptees (four females, ages 27 to 36, and five males, ages 31 to 37) – all of them biological children of the biological parents of the bipolar adoptees. Of these nine biological sibs, seven had not been separated from their biological family, while two had been given away for adoption in other adoption families. The results of the psychopathological examination in sibs of bipolar adoptees are given in Table VI. There are three bipolar patients, two unipolar patients, and one cyclothymic patient in the biological sibs, compared with no bipolar and one unipolar case in the adoptive sibs. The overall rate of psychopathology was 66% in biological sibs and 8% in the adoptive sibs, the difference being made up exclusively by patients suffering from affective spectrum disorder. These data in sibs also emphasise the importance of the genetic factor in the transmission of manic–depressive illness.

TABLE VI
Diagnosis in sibs of bipolar adoptees (n = 029)

	Sibs	
	Adoptive n = 12	*Biological n = 9*
Bipolar	0	3
Unipolar	1	2
Schizoaffective	0	0
Cyclothymic	0	1
Affective spectrum	1 (8%)	6 (66%)
Schizophrenia	0	0
Alcoholism	0	0
Sociopathy	0	0
All psychopathology	1 (8%)	6 (66%)

Another finding of interest is that no father-to-son transmission of bipolar illness was seen in our entire sample; this is consistent with a sex-linked model of bipolar illness. As would be expected, bipolar illness had an early onset in all parents in whom it was present; but the onset of unipolar illness in the adopting parents occurred, in every case, after the onset of manic–depressive illness in their children, whereas in the biological parents, onset of unipolar disease occurred almost always before the onset in their children. This observation strengthens the genetic hypothesis by suggesting that the adoptive parents' unipolar illness might be more reactive and less severe than that of their biological counterparts; early onset is often considered to be an index of severity in psychiatric disorder.

Linkage studies

A number of studies have reported that the O blood group is most frequently found in manic–depressive patients (Barker *et al*, 1961; Mendlewicz & Rainer, 1974). This potential association between a blood group factor and a major psychosis, although poorly understood, may indicate that the ABO genotype plays a role in the predisposition to manic–depressive illness. Association between traits is not to be confused with linkage, i.e. the proximity of two traits on the same chromosome, resulting in their dependent assortment during the process of meiosis. In this

method, one tries to test a potential linkage relationship between a known genetic marker and a character which is known to be genetically determined, but which has not yet been mapped on the chromosomes; it has been used successfully in the genetic study of several hereditary conditions, and recently to test the hypothesis of genetic linkage in manic–depressive illness. Linkage to HLA antigens has recently been suggested (Wirtkamp *et al*, 1981) for bipolar illness, but not confirmed in another study (Targum *et al*, 1979). Reich *et al* (1969) studied two large families assorting for colour blindness (an X-linked recessive marker) and bipolar illness, while Mendlewicz *et al* (1972*a*,*b*) reported on seven such families; in both studies, the marker and the illness failed to show independent assortment. Winokur & Tanna (1969) described three more families, assorting in a dependent fashion for manic–depressive illness and the Xg blood group (a dominant X-linked marker). Mendlewicz *et al* (1975) confirmed these results in 11 other families assorting for the Xg blood group and the illness. Mendlewicz & Fleiss (1974) were able to demonstrate close linkage between bipolar illness and both deutan and protan colour blindness in 17 informative pedigrees. (Deutan colour blindness is a deficiency of green perception; protan is a deficiency of red perception. The chromosomal loci of these two conditions are closely linked, but not identical.)

Linkage between bipolar illness and the Xg blood group, although measurable, was found to be less close in 23 informative families. Recent linkage data from our laboratory confirm a linkage relationship between colour blindness and bipolar manic–depressive illness (Mendlewicz *et al*, 1979), and are at variance with the report of Gershon *et al* (1979), who did not find such a linkage. A more comprehensive study – part of the Biological Psychiatry Collaborative Programme of the World Health Organization – was conducted in four collaborative centres (Bethesda, Basel, Brussels and Copenhagen) on 16 informative families, the overall results being consistent with the presence of linkage between bipolar illness and colour blindness. Some families showed an X-linked pattern of inheritance, while others did not, this last observation suggesting the hypothesis of genetic heterogeneity in manic–depressive illness (Gershon *et al*, 1980). Figure 1 illustrates the distribution of deuteranopia and bipolar–unipolar disorders in successive generations of a family informative for the analysis of linkage between colour blindness and affective illness.

Mendlewicz *et al* (1980) reported a positive linkage between bipolar illness and glucose-6-phosphate dehydrogenase deficiency (G6PD), which is a genetic marker on the X-chromosome. Recently Del Zompo *et al* (1984) have studied two pedigrees for bipolar illness, colour blindness, and G6PD deficiency, which is closely linked with colour blindness on the X-chromosome (Siniscalco, 1964). Their results are also consistent with an X-linkage in bipolar illness. Like Kruger *et al* (1982), Risch & Baron (1982) suggested genetic heterogeneity to explain discrepancies in X-linkage studies.

Table VII summarises the sex distribution in first-degree relatives of bipolar probands in some recent studies, most of which show a clear excess of females in the relatives of bipolar probands. However, other investigators have failed to find a preponderance of affected females, as compared to males, in first-degree relatives. Moreover, some family studies have shown a male-to-male transmission of the disease (Perris, 1968; Brown *et al*, 1973; Goetzl *et al*, 1974). Mendlewicz & Rainer (1974) observed the same phenomenon in about 10% of their overall sample, though it is nevertheless a rare event in the kindreds of bipolar probands (Mendlewicz, 1986). Thus, it seems quite clear that more than one genetic entity is involved in bipolar illness.

We have recently collected new data on eight informative families assorting for manic–depressive illness and a DNA restriction fragment length

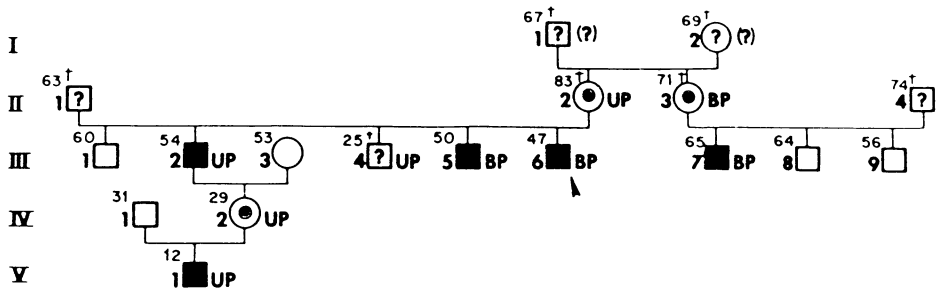

FIG. 1.

TABLE VII
Percentage of affectively ill in first-degree relatives of bipolar patients

Study	*Year*	*Total*	*M (%)*	*F (%)*
Winokur *et al*	1982	40	15 (38)	25 (63)
Mendlewicz & Rainer	1974	229	93 (40)	136 (60)
Winokur *et al*	1969	76	20 (26)	56 (74)
Kadrmas *et al*	1979	102	54 (65)	48 (47)
Stenstedt	1952	41	19 (47)	22 (53)
Angst *et al*	1980	38	15 (39)	23 (61)
Mendlewicz & Rainer	1977	29	9 (31)	20 (69)
Gershon *et al*	1978	79	38 (48)	41 (52)
Taylor & Abrams	1981	36	11 (31)	25 (69)
James & Chapman	1975	52	13 (25)	39 (75)
Goetzl *et al*	1974	35	13 (37)	22 (63)
Gershon *et al*	1975	36	20 (55)	16 (45)
Iowa Collaborative Study	1983	54	22 (41)	32 (59)
Total		847	342 (39)	505 (61)

From Winokur & Crowe (1983).

polymorphism (RFLP), corresponding to the factor IX locus at the subtelomeric region of the X-chromosome long arm; this RFLP has recently been shown to be associated with haemophilia B (or Christmas disease). Clear evidence emerged in favour of linkage between this new X-linked genetic probe and bipolar affective illness (Mendlewicz *et al*, 1987), but the findings did not support the report of possible linkage between MDI and a locus on chromosome II in one Amish family (Egeland *et al*, 1987) which was not replicated in three Icelandic and three North American families (Hodgkinson *et al*, 1987; Detera-Waldeigh *et al*, 1987).

Thus, among the most relevant family studies of bipolar affective disorders, a majority of the reports show a sex ratio distribution of affective illness in first-degree relatives (excess of females over males) compatible with an X-linked dominant transmission. Investigation of male-to-male transmission of bipolar illness reveals that this pattern of inheritance, if not absent, is nevertheless a rare event in the kindreds of bipolar probands. Furthermore, the great majority of linkage studies are conclusive in demonstrating the presence of linkage between bipolar manic depressive psychosis and several X-linked genetic markers, in a subgroup of bipolar illness; new evidence using DNA recombinant methods substantiates this form of X-linked dominant transmission of bipolar illness. Clearly, other forms of affective disorders are not transmitted through the X-chromosome, and a major gene transmission for manic depression on chromosome II has been implicated in Amish families, which may indicate that genetic heterogeneity is present in bipolar illness. Studies investigating the clinical characteristics and therapeutic response of the X-linked form of bipolar illness are at present being carried out. Future implications of DNA research strategies in affective disorders, and research in relation to X-linkage in manic–depression, include the study of the relationship between the fragile X phenotype and affective disorders (Pascalis *et al*, 1985; Reiss *et al*, 1986) and biochemical investigation of relevant trace markers, such as the binding of serotonin receptors, which has recently been shown to be sex-influenced (Fischette *et al*, 1983).

Mode of transmission

There is no final consensus on the types of genetic mechanisms that operate in affective illness: too little is known about the genetics of unipolar and schizoaffective illness even to propose specific genetic models for these syndromes. It is also difficult, if not impossible, to draw definite conclusions yet on the mode of inheritance of bipolar manic–depressive illness; bias in selecting study populations must be carefully avoided while clinical or genetic heterogeneity may foil the attempt to come to an unequivocal conclusion. There are, however, certain genetic models that can already be ruled out from the available genetic data. Autosomal (non-sexual chromosome) recessive inheritance is one of these, since it cannot account for the appreciable number of families showing two- and three-generation transmission of the illness. There is no increase in the morbid risks in sibs or consanguinity (i.e. unions between cousins), which would be expected under recessive inheritance. Sex-linked recessive inheritance is also very unlikely, because there are no studies so far reporting an excess

of affected males over affected females, which is always present in sex-linked recessive transmission; in fact, the opposite has generally been observed.

There are some arguments in favour of a major dominant type of inheritance: (a) the illness has often been observed to be present in successive generations; (b) the morbidity risks in parents, sibs, and children are similar, and some studies have shown the risks in sibs of probands with no affected parents to be equal to the risks in sibs with one affected parent (Winokur *et al*, 1969; Mendlewicz & Fleiss, 1974); (c) when we tested our own data for consistency with a single-gene threshold model the observed values for sibs and parents were compatible with various forms of single-gene inheritance, with dominant inheritance most likely (Mendlewicz & Rainer, 1974). Single-factor inheritance is consistent with these data. Some investigators have postulated a major autosomal dominant gene with reduced penetrance (expressivity) for bipolar disorder (Strömgren, 1938; Stenstedt, 1952; Kallmann, 1954). This autosomal hypothesis has the value of simplicity, and fits most of the data except for the sex ratio differences found in patients and relatives – a preponderance of affected females.

Polygenic inheritance in bipolar manic–depressive illness has also been suggested by other investigators who used a computational model to test ancestral secondary cases for polygenic versus monogenic inheritance (Perris, 1972; Slater *et al*, 1972). However, another study using the same method has shown that one subgroup of the illness conformed to a monogenic model, while a second subgroup behaved as a polygenic entity (Mendlewicz *et al*, 1972*a*). Finally, the linkage studies described above contribute strong evidence pointing to an X-linked dominant gene involved in the transmission of some manic–depressive illness; another family study (Taylor & Abrams, 1974) arrived at the same conclusion for early onset forms of bipolar illness.

It is argued, however, that there are families where male-to-male transmission of the disease is apparent – an observation incompatible with X-linkage (Perris, 1968; Goetz *et al*, 1974). This is also the case in our own material (Mendlewicz & Rainer, 1974), where these families represented about 10% of the overall sample. Furthermore, the preponderence of affected females, compared with males, in first-degree relatives (Angst, 1966; Winokur *et al*, 1969; Mendlewicz & Rainer, 1974; Taylor & Abrams, 1974) of bipolar patients is far from a universal finding (Perris, 1968; Brown *et al*, 1973; Goetz *et al*, 1974).

The question of male-to-male transmission of affective illness is not easy to evaluate since many former studies did not provide data on assortative mating, which makes it difficult to assess the possibility of gene transmission through the mothers' side of the family. In our own linkage studies, the rarity of kindreds with father-to-son transmission of the illness is due to the ascertainment method selecting primarily informative families for X-linkage analysis. A recent linkage study conducted in Israel using classical genetic markers such as colour blindness and G6PD deficiency confirmed the presence of an X-linked form of manic–depression and reported that about 30% of the families investigated showed no male-to-male transmission and were X-linked (Baron *et al*, 1987).

An interesting approach to the problem has recently been proposed by Crowe & Smouse (personal communication); working on Winokur's data, they derived an age-dependent penetrance function for manic–depressive illness, and their analysis revealed that a sex-linked dominant model was far more likely to explain the data than an autosomal dominant one.

Although the X-linked dominant model appears to be an important mode of transmission of manic–depressive illness, it seems quite clear that more than one genetic entity is involved in this disease.

The relative frequency of the X-linked form of bipolar illness in the general population is an important issue which has remained unknown until now, and deserves further epidemiological genetic investigation.

References

ANGST, J. (1966) *Zur Atiologie und Nosologie endogener depressiver Psychosen*. Monographien aus dem Gesamtgebrete der Neurologie und Psychiatrie. Berlin: Springer.

BARKER, J. B., THEILLIE, A. & SPIELBERGER, C. D. (1961) Frequency of blood types in an homogenous group of manic–depressive patients. *Journal of Mental Science*, **107**, 936–942.

BARON, M., RISH, N., HAMBURGER, R. *et al* (1987) Genetic linkage between X-chromosome markers and bipolar affective illness. *Nature*, **326**, 289–292.

BERTELSEN, A., HARVALD, B. & HAUGE, M. (1977) A Danish study of manic–depressive disorders. *British Journal of Psychiatry*, **130**, 330–351.

BÖÖK, J. A. (1953) A genetic and neuropsychiatric investigation of a North-Swedish population. *Acta Geneticae Medica et Genellologiae*, **4**, 1–100.

BROWN, R. J., ELSTON, R. C., POLLITZER, W. S., PRANGE, A. & WILSON, E. (1973) Sex-ratio in relatives of patients with affective disorder. *Biological Psychiatry*, **6**, 307–309.

CADORET, R. J. (1978) Evidence for genetic inheritance of primary affective disorder in adoptees. *American Journal of Psychiatry*, **134**, 463–466.

COOPER, J. E., KENDALL, R. E., GURLAND, B. J., SHARP, L., COPELAND, J. R. M. & SIMON, R. (1972) *Psychiatric diagnosis in New York and London*. New York: Oxford University Press.

Da Fonseca, A. F. (1959) Analise heredo-clinica das perturbacoes affectivas. Dissertation, University of Porto.

Del Zompo, M., Bocchetta, A., Goldin, L. R. & Corsini, G. U. (1984) Linkage between X-chromosome markers and manic depressive illness, two Sardinian pedigrees. *Acta Psychiatrica Scandinavica*, **70**, 282–287.

Detera-Waldeigh, S. D., Berretini, W. H., Goldin, L. R., Boorman, D., Anderson, S. B. & Gershon, E. S. (1987) Close linkage of C-Harvey-ras-1 and the insulin gene to affective disorder is ruled out in three North American pedigrees. *Nature*, **325**, 806–808.

Egeland, J. A., Gerhard, D. S., Pauls, D. L., Sussex, J. S., Kidd, K. K., Allen, C. R., Hostetter, A. H. & Housman, D. E. (1987) Bipolar affective disorders linked to DNA markers on chromosome 11. *Nature*, **325**, 783–787.

Fischette, C. T., Biegon, A. & McEwan, B. S. (1983) Sex differences in serotonin receptor binding in rat brain. *Science*, **222**, 333–335.

Gershon, E. S., Targum, S. D., Matthysse, S. & Bunney, W. E., Jr (1979) Color blindness not closely linked to bipolar illness. *Archives of General Psychiatry*, **36**, 1423–1431.

——, Mendlewicz, J., Gastpar, M., Bech, P., Goldin, L. R., Koeholz, P., Rafaelson, O. J., Vartanian, F. & Bunney, W. E., Jr (1980) A collaborative study of genetic linkage of bipolar manic-depressive illness and red/green colour blindness. *Acta Psychiatrica Scandinavica*, **61**, 319–338.

Goetzl, V., Green, R., Whybrow, P. & Jackson, R. (1974) X-linkage revisited. A further family study of manic-depressive illness. *Archives of General Psychiatry*, **31**, 665–672.

Harvald, B. & Hauge, M. (1965) Hereditary factors eludicated by twin studies. In *Genetics and the Epidemiology of Chronic Diseases* (eds J. V. Neel, M. W. Shaw & W. J. Schull). Washington, DC: US Department of Health, Education and Welfare.

Helgasson, T. (1964) Epidemiology of mental disorders in Ireland. *Acta Psychiatrica Scandinavica*, **173** (Suppl.), 1–258.

Hodgkinson, S., Sherrington, R., Gurling, H., Marchbanks, R., Reeders, S., Mallet, J., McInnes, M., Petursson, H. & Brynjolson, J. (1987) Molecular genetic evidence of heterogeneity in manic-depression. *Nature*, **325**, 805–806.

Kallmann, F. J. (1954) Genetic principles in manic-depressive psychoses. In *Depression* (P. Hoch & J. Zubin). New York: Grune & Stratton.

Kringlen, E. (1967) *Heredity and environment in the functional psychoses. An epidemiological-clinical twin study*. Oslo, Norway: Universitstoforlaget.

Kruger, S. D., Turner, J. W. & Kidd, K. K. (1982) The effects of requisite assumptions on linkage analyses of manic-depressive illness with HLA. *Biological Psychiatry*, **17**, 1081–1099.

Leonhard, K. (1959) *Aufteilung der Endogenen Psychosen*. Berlin: Akademie-Verlag.

Mendlewicz, J. (1986) X-linked inheritance in affective disorders. In *Psychiatry, the state of the art. Vol. 2. Biological psychiatry, higher nervous activity* (eds P. Pichot, P. Berner, R. Wolf & K. Thau).

—— & Baron, M. (1981) Morbidity risks in subtypes of unipolar depressive illness; differences between early and late onset forms. *British Journal of Psychiatry*, **139**, 463–466.

—— & Fleiss, J. (1974) Linkage studies with X-chromosome markers in bipolar (manic-depressive) and unipolar (depressive) illness. *Biological Psychiatry*, **9**, 261–294. (Abstracted in Excerpta Medica, Psychiatry, 32, 3, 142, 1975).

—— & Rainer, J. D. (1974) Morbidity risk and genetic transmission in manic-depressive illness. *American Journal of Human Genetics*, **26**, 692–701.

—— & —— (1977) Adoption study supporting genetic transmission in manic-depressive illness. *Nature*, **268**, 327–329.

——, Fieve, R. C., Rainer, J. D. & Fleiss, J. L. (1972*a*) Manic-depressive illness; a comparative study of patients with and without a family history. *British Journal of Psychiatry*, **120**, 523–530.

——, Fleiss, J. L. & Fieve, R. R. (1972*b*) Evidence for X-linkage in the transmission of manic-depressive illness. *Journal of the American Medical Association*, **222**, 1627.

——, Massart-Guiot, T., Wilmotte, J. & Fleiss, J. L. (1974) Blood groups in manic-depressive illness and schizophrenia. *Diseases of the Nervous System*, **35**, 39–41.

——, Fleiss, J. L. & Fieve, R. R. (1975) Linkage studies in affective disorders: the Xg blood group in manic-depressive illness. In *Genetics and psychopathology* (eds R. R. Fieve, D. Rosenthal & H. Bril). Baltimore: Johns Hopkins Press.

——, Linkowski, P., Guroff, J. J. & Van Praag, H. M. (1979) Colour blindness linkage to bipolar manic-depressive illness. New evidence. *Archives of General Psychiatry*, **36**, 1442–1447.

——, Linkowski, P. & Wilmotte, J. (1980) Linkage between glucose-6-phosphate dehydrogenase deficiency and manic-depressive psychoses. *British Journal of Psychiatry*, **137**, 337–342.

——, Simon, P., Charon, F., Brocas, S., Legros, & Vassart, G. (1987) Polymorphic DNA marker on X chromosome and manic-depression. *The Lancet*, 1230–1232.

Ministry of Health (1969) *Statistical report series, No. 4*. Psychiatric hospitals and units in England and Wales, in-patients statistics from the mental health enquiry for the years 1964, 1965 and 1966. London: Her Majesty's Stationery Office.

Pascalis, G., Teyssier, J. R., Carre-Pigeon, F. (1985) Presence d'un Xq-fra chez un maniaque; situation du gene de la PMD sur le bras long du chromosome X. *Annales Medico-Psychologiques*, **146**, 594–595.

Perris, C. (1968) Genetic transmission of depressive psychoses. *Acta Psychiatrica Scandinavica*, **203** (Suppl.), 45–52.

—— (1972) Abnormality on paternal and maternal sides: observations in bipolar manic-depressive and unipolar depressive psychosis. *British Journal of Psychiatry*, **118**, 207–210.

Price, J. (1968) The genetics of depressive behaviour. In *Recent developments in affective disorders* (eds A. Coppen & A. Walk). British Journal of Psychiatry, Special Publication No. 2.

Reich, T., Clayton, P. J. & Winokur, G. (1969) Family history studies: V. The genetics of mania. *American Journal of Psychiatry*, **125**, 1358–1359.

Reiss, A. L., Feinstein, C., Toomey, K. E., Goldsmith, B., Rosenbaum, K. & Caruso, M. A. (1986) Psychiatric disability associated with the fragile X chromosome. *American Journal of Medical Genetics*, **23**, 393–401.

Risch, N. & Baron, M. (1982) X-linkage and genetic heterogeneity in bipolar-related major affective illness; re-analysis of linkage data. *Annals of Human Genetics*, **46**, 153–166.

Rosanoff, A. J., Handy, L. M. & Rosanoff-Plessett, I. B. A. (1934) The etiology of manic-depressive syndromes with special reference to their occurrence in twins. *American Journal of Psychiatry*, **91**, 725–762.

Rudin, E. (1923) Ubert Vererbung geistiger Storungen. *Zeitschift fur die Gesamte Neurologie und Psychiatrie*, **81**, 459–496.

Siniscalco, M., Filippi, G. & Latte, B. (1964) Recombination between protan and deutan genes; data on their relative positions in respect of the G6PD locus. *Nature*, **204**, 1061–1064.

Slater, E. (1953) *Psychotic and neurotic illness in twins*. Special Report. Medical Research Council Series, 178. London: Her Majesty's Stationery Office.

Slater, E., Maxwell, J. & Price, J. S. (1972) Distribution of ancestral secondary cases in bipolar affective disorders. *British Journal of Psychiatry*, **118**, 215–218.

Stenstedt, A. (1952) A study in manic-depressive psychoses. *Acta Psychiatrica et Neurologica Scandinavica* (Suppl.), **79**.

Stromgren, E. (1938) *Beitrage zur psychiatrischen Erblehere*. Copenhagen: Munksgaart.

Swanson, D. A. (1960) Suicide in identical twins. *American Journal of Psychiatry*, **116**, 934–935.

TARGUM, S. D., GERSHON, E. J., VAN EERDEWEGH, M. & ROGENLINE, N. (1979) Human leucocyte antigen (HLA) system not closely linked to or associated with bipolar manic-depressive illness. *Biological Psychiatry*, **14**, 615–636.

TAYLOR, M. & ABRAMS, R. (1974) Manic states. A genetic study of early and late onset of affective disorders. *Archives of General Psychiatry*, **28**, 656–672.

TOMASSON, H. (1938) Further investigations on manic-depressive psychoses: investigations on heredity in Ireland. *Acta Psychiatrica et Neurologica Scandinavica*, **13**, 517–526.

TORGERSEN, S. (1986) Genetic factors in moderately severe and mild affective disorders. *Archives of General Psychiatry*, **43**, 222–226.

WILMOTTE, J. (1980) Linkage between glucose-6-phosphate dehydrogenase deficiency and manic depressive psychoses. *British Journal of Psychiatry*, **137**, 337.

WINOKUR, G. & CROWE, R. R. (1983) Bipolar illness. The sex-polarity effect in affectively ill family members. *Archives of General Psychiatry*, **40**, 57–58.

—— & TANNA, V. L. (1969) Possible role of X-linked dominant factor in manic-depressive diseases. *Diseases of the Nervous System*, **30**, 89–94.

——, CLAYTON, P. J. & REICH, T. (1969) *Manic-depressive illness*. St Louis: C. V. Mosby.

WIRTKAMP, L. R., STANCER, H. C., PERSAD, E., FLOOD, C. & GUTTORSMEN, S. (1981) Depressive disorders and HLA. A gene on chromosome 6 that can affect behaviour. *New England Journal of Medicine*, **305**, 1301–1306.

ZERBIN-RÜDIN, E. (1967) Endogene Psychosen. In *Human-Genetik: ein Kurzs Handbuch in Fünf Banden* (ed. P. E. Becker) vol. 2. Stuttgart: Thieme.

—— (1969) *Zur Genetik der Depressiven Erkrankungen*. In *Das Depressive Syndrom* (eds H. Hippius and H. Selbach). Munich: Urban & Schwarsenberg.

J. Mendlewicz, *Chef de Service, Service de Psychiatrie, Hopital Erasme, Cliniques Universitaires de Bruxelles, Belgium*