A FAMILY AND GENETIC STUDY OF PRIMARY AFFECTIVE DISORDERS

GURMEET SINGH*, M.B.B.S., M.R.C. Psych., D.P.M. (Lond.), Dip. Psychiat. (McGill), Dip. Am. Board Psychiat. & Neurology.
M. L. AGARWAL, M.B.B.S., M.D.

The unitary concept of manic-depressive psychoses as originally proposed by Kraepelin (1921) has been questioned by recent investigators such as Leonhard (1965) and Perris (1966), who have presented clinical and genetic evidence to suggest that it is a heterogeneous group consisting of two distinct types—(a) the unipolar which is characterised by recurrent episodes of depression only, and (b) the bipolar in which both manic and depressive episodes occur. Among the unipolar group, Woodruff et al. (1971) and Winokur et al. (1971, 1975) claim to have further distinguished two subtypes based on observed differences in family history between patients developing their first illness before the age of 40 yrs.—the depressive spectrum disease; and after the age of 40 yrs.—the pure depressive disease.

Evidence for a genetic contribution to the etiology of primary affective disorders comes from both twin and family studies and has been summarised by Slater and Cowie (1971), and Gershon et al. (1975a). The work of Leonhard (1966), Angst (1966), and Perris (1966) have all provided data supporting the division into the unipolar and bipolar groups—each with its distinct genetic mechanism. Winokur and Tana (1969), on the basis of (a) the occurrence of bipolar illness in successive generations, (b) a preponderance of female affected relatives of bipolar probands, and (c) the rarity of father to son transmission, have suggested the possibility of a single dominant gene located on the X chromosome in the bipolar group. However, other workers are not in agreement with this (Gershon et al., 1975b and Smeraldi et al., 1977) although confirming the importance of genetic factors, suggest that bipolar and unipolar illness probably represent different thresholds on a continuous spectrum or scale of liability to affective disorders in which the bipolar form, because of its earlier age of onset and higher risk in relatives be considered a more severe form than unipolar illness.

Winokur (1972) suggested the possibility of a second genetic factor—probably autosomal dominant—that may be more explicitly related to the expression of mania rather than the X-linked factor which may generally predispose the individual to an Affective illness (either unipolar or bipolar). Perris (1966) has also supported an X-linked transmission, but only in the unipolar group. Zerbin-Rudin (1968) in a review of twin studies, showed that a high proportion of pairs of monozygotic twins, both of whom had an Affective illness, were such that one member suffered from a unipolar illness and the other from a bipolar illness; suggesting that they either have a common genetic basis, or that the individuals personality or environment in some way affects the outward expressivity of the bipolar genotype. Perris (1971) and Slater et al. (1971) using a computational model based on maternal and paternal incidence figures have reported data consistent with a polygenic pattern of inheritance for Affective illnesses. Finally, there is one report-Venkoba Rao (1974) who on the basis of a clinical study of 101 patients of...
endogenous depression concluded that there was no significant difference between the unipolar and bipolar affective disorders. However, this study is not strictly comparable since he did not calculate the morbidity risk for affective illness in all first degree relatives but based his conclusions only on the presence or absence of a history of affective illness or suicide among the parents and sibs of the probands.

AIMS

1. To estimate the morbidity risk for affective illness, alcoholism, and sociopathy in the first degree relatives of probands with unipolar and bipolar illness.

2. To evaluate whether the family data supports the separation of unipolar and bipolar illness as two distinct entities; as also the subdivision of unipolar group into the early onset and late onset types.

3. To compare these findings with current genetic hypotheses.

MATERIAL AND METHODS

The present report is based on a detailed clinical and family history study of 100 probands with primary affective psychosis—57 bipolar and 43 unipolar—admitted to the psychiatry unit of Rajendra Hospital, Patiala. There was a total of 830 first degree relatives of these probands (including parents, sibs, and children). All available relatives were interviewed personally, and in case of those who could not be present personally, details were elicited from the patient and other relatives.

Diagnostic criteria: In addition to a primary diagnosis of Manic Depressive Psychosis (I.C.D.8), all probands had to fulfill the diagnostic research criteria for primary Affective Disorder as proposed by Feighner et al. (1972). To designate a patient as suffering from a unipolar illness, it was considered necessary to adopt a familial definition as suggested by Winokur et al. (1971). Thus the criteria employed were: (a) history of at least two definite depressive episodes requiring hospitalization or treatment by a psychiatrist, and (b) absence of a history of mania—both in the patient and among the first degree relatives. These are similar to the criteria used by Mandlewicz and Reiner (1968), and Johnson and Leeman (1977). A diagnosis of mania at the time of index admission or a history of mania in the past was required for inclusion in the bipolar group.

No one was admitted to the study as proband who had evidence of a pre-existing non-affective psychiatric illness, or had any medical illness, or was using drugs known to cause depression. The diagnostic criteria for affective illness in the first degree relatives were essentially the same as for the probands. The morbidity risk was estimated by the abridged method of Weinberg (1925) as described by Stenstedt (1952). The formula is follows:

\[ M.R. = \frac{a}{b - b_0 - 1/2b_m} \]

where,

- \( a \) = the number of affected individuals
- \( b \) = the total number of members in the family
- \( b_0 \) = the number of persons who have not yet reached the risk period
- \( b_m \) = the number of individuals passing through the risk period.

The risk period for Affective illness used in the present study was between fifteen to sixty five years.

RESULTS

Table 1 shows the age and sex distribution as well as the age of onset of illness for all 100 probands, consisting of 56 males and 44 females. When broken down by polarity, it is seen that of the 57 bipolar probands, 40 (70.2%) are males and only 17 (29.8%) are females. Among the uni-
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Table I—Showing age and sex distribution and age of onset of all probands

| Age group | Bipolar age | Unipolar age |
|-----------|-------------|--------------|
|           | M | F | Total | M | F | Total | M | F | Total |
| 10—19     | 5 | 5 | 10    | 12 | 7 | 19    | 2 | 1 | 3    |
| 20—29     | 17 | 2 | 19    | 17 | 3 | 20    | 4 | 8 | 12   |
| 30—39     | 6 | 3 | 9     | 7 | 6 | 13    | 3 | 6 | 9    |
| 40—49     | 8 | 7 | 15    | 2 | 1 | 3     | 5 | 6 | 11   |
| 50—59     | 3 | 0 | 3     | 2 | 0 | 2     | 1 | 4 | 5    |
| 60—69     | 1 | 0 | 1     |     |   |     | 1 | 2 | 3    |
|           | 40 | 17 | 57   |     |   |     | 16 | 27 | 43  |

Table 2—Morbid risk for affective disorder in first degree relatives of bipolar and unipolar probands

| Relative | Bipolar | Unipolar |
|----------|---------|----------|
|          | Total   | BZ       | No. 111 | M.R.   | Total   | BZ       | No. 111 | M.R.   |
| Parents  | 114     | 103.0    | 20      | 19.4   | 86      | 76.0     | 16      | 20.7   |
| Sibs     | 218     | 127.5    | 29      | 22.7   | 149     | 109.5    | 30      | 27.4   |
| Children | 123     | 40.0     | 4       | 10.0   | 140     | 45.5     | 9       | 19.8   |
| Total    | 455     | 270.5    | 53      | 19.6   | 375     | 231.0    | 55      | 23.8   |

Polar patients on the other hand, we find a greater number of females-27 (63%) as compared to males-16 (37%). This difference is highly significant ($x^2=11.62, p <0.001$).

The age of all probands in the present study was between 15 to 65 years. The mean age for the bipolar group is 33.6 years, and for unipolar group is 39.5 years. However, a closer examination reveals a slight excess of bipolar probands in the earliest age groups, which is partly explained by the fact that many of these patients were suffering from a manic illness and hence qualified for inclusion in the study even though it was their first illness. Whereas the criterion of at least two depressive episodes for inclusion as a unipolar proband would tend to raise the average in the latter group.

An analysis of the age of onset of first illness shows that while 90% of the bipolar probands have had their first attack before reaching the age of 40 years, the corresponding figure among unipolar probands is 72%. This just fails to reach the 1% level of significance ($x^2=6.36, p<0.02$), suggesting an earlier age of onset for bipolar illness.

Table 2 shows the total number of relatives in each category i.e. parents, sibs, and children, the corrected number at risk (Bezugsziffer), the number ill, and the morbid risk for affective disorder in the first degree relatives of bipolar and unipolar probands. In the bipolar group, the morbid risk of 19.4 for parents, and 22.7 for sibs, is similar to those reported by other workers. However, the estimated risk for
children (10.0) is rather low and may be related to the comparatively younger age of the probands so that a majority of the children had not yet reached the risk period. Hence the small numbers of ill subjects at the time of the study is likely to give an underestimate of the actual morbid risk. In the unipolar group, the morbid risk for affective illness is 20.7 for parents, 27.4 for sibs., and 19.8 for children. The cumulative risk for all relatives is 23.8.

Table 3 and 4 shows a comparison of our findings with those previously reported in the literature. In the bipolar group the total morbid risk for affective illness (not including doubtful affective illness or suicide) in the first degree relatives is 19.6. This is in agreement with the figures reported by Angst (1966), Perris (1966), and James and Chapman (1975); although somewhat higher than those of Terebiatowska (1977), Smeraldi et al. (1977), and Gershon et al. (1975). In the unipolar group the risk figure found in the present study (23.8) is higher than all previously reported studies, most of which give risk values ranging from a low of 11.7 (Angst, 1966) to a high of 15.4 (Winokur et al., 1971). The raised morbid risk is seen in all categories of relatives, but is most marked among the sibs. of probands (Table 4).

Table 5 shows the morbid risk for alcoholism and sociopathy in addition to the risk for affective disorder separately for male and female relatives, for both the bipolar and unipolar probands. A diagnosis of alcoholism was made in 6 first degree relatives of bipolar probands, giving a morbidity risk of 4.0. All six were males, so that when comorbidity with the risk for depressive

| Author                        | Parents | Sibs. | Child. | Total risk | Bipolar | Unipolar | Suicide |
|-------------------------------|---------|-------|--------|------------|---------|----------|---------|
| **Table 3—Morbidity risk for affective disorders in first degree relatives of bipolar probands** |
| Angst (1966)                  | 14.4    | 21.5  | ..     | 21.0       | 3.7     | 11.2     | 3.1     |
| Perris (1966)                 | 16.0    | 23.0  | ..     | 20.0       | 10.8    | 0.58     | 8.6     |
| James & Chapman (1975)        | ..      | ..    | ..     | 18.8       | 6.4     | 13.2     | ..      |
| Gershon et al. (1975)         | ..      | ..    | ..     | 10.6       | 3.8     | 6.7      | ..      |
| Terebiatowska (1977)          | 15.1    | 16.9  | ..     | 16.9       | ..      | ..       | ..      |
| Smeraldi (1977)               | ..      | ..    | ..     | 16.8       | 5.8     | 7.1      | 3.9     |
| Present study (1978)          | 19.4    | 22.7  | 10.0   | 19.6       | 5.5     | 14.0     | 1.1     |

| Author                        | Parents | Sibs. | Child. | Total risk | Bipolar | Unipolar | Suicide |
|-------------------------------|---------|-------|--------|------------|---------|----------|---------|
| **Table 4—Morbidity risk for affective disorder in first degree relatives of unipolar probands** |
| Angst (1966)                  | 11.2    | 12.2  | ..     | 11.7       | 0.29    | 9.1      | 2.3     |
| Perris (1966)                 | 13.9    | 13.0  | ..     | 14.6       | 0.85    | 7.4      | 6.8     |
| Winokur (1971)                | ..      | ..    | ..     | 15.4       | ..      | ..       | ..      |
| Gershon et al. (1975)         | ..      | ..    | ..     | 13.6       | 2.1     | 11.5     | ..      |
| Terebiatowska (1977)          | 12.0    | 11.4  | ..     | 12.5       | ..      | ..       | ..      |
| Smeraldi (1977)               | ..      | ..    | ..     | 12.9       | 0.6     | 8.0      | 4.3     |
| Present study (1978)          | 20.7    | 27.4  | 19.8   | 23.8       | ..      | ..       | ..      |
TABLE 5—Morbidity risk for affective illness and alcoholism in first degree male and female relatives

|                      | Affective | Alcohol | Total |
|----------------------|-----------|---------|-------|
| **Bipolar Probands** |           |         |       |
| M. R. for all male relatives | 19.4      | 4.0     | 22.6  |
| M. R. for all female relatives | 19.6      |         | 19.6  |
| **Unipolar Probands** |           |         |       |
| M. R. for all male relatives | 15.0      | 12.4    | 25.5  |
| M. R. for all female relatives | 31.5      |         | 31.5  |

All unipolar probands were then divided into an early onset group (first illness before the age of 40 yrs.) and a late onset group (first illness after the age of 40 yrs.). The cumulative morbidity risk for all first degree relatives in higher for the early onset probands—26.3, as compared to the late onset group—18.7. Analysing the morbid risks for male and female relatives separately we find that the risk for both Affective disorders as well as alcoholism among the male relatives is practically the same in both the early onset and late onset groups—14.8 and 13.7 for depression, and 12.4 and 11.3 for alcoholism, giving a total morbid risk of 25.0 and 22.2 respectively (Table 6). The difference between the early and late onset groups being almost entirely due to a higher morbid risk among female relatives of early onset probands as compared to the late onset probands (36.4 vs. 23.0).
However, a more striking is that although the total morbid risk for first degree relatives of early onset unipolar probands (26.3) is considerably higher than the rate for late onset unipolar probands (18.7) (which is in fact closer to the bipolar group -19.5); there is a marked preponderance of affectively ill female first degree relatives in both the early onset and late onset groups. For the early onset group, the M. R. for female relatives is 36.4 as compared to only 14.8 for males. \( \chi^2 = 22.56, \text{df}=1, p<0.001 \); and for the late onset group the M. R. for female relatives is 23.0 as compared to 13.7 for male relatives. \( \chi^2 = 5.43, \text{df}=1, p<0.02 \).

In summary, the following findings of the present study lend support to the validity of the clinical division of the primary affective disorders into the unipolar and bipolar groups:

1. The male-female ratio in probands of bipolar illness is 1: 0.43, whereas in the unipolar group it is 1: 1.6, showing a marked excess of females suffering from a unipolar illness and males from a bipolar illness.

2. The morbid risk for affective disorder among male and female first degree relatives of bipolar probands is almost identical (19.4 and 19.6). In the unipolar group on the other hand, the risk for female relatives is approx. twice that for male relatives (31.5 versus 15.0).

3. The morbid risk for alcoholism and sociopathy among first degree relatives of bipolar probands is low (M. R. 4.0), and probably not very different from that in the general population (Lal and Singh, 1978). In the unipolar group we find a striking increase in the risk for alcoholism and sociopathy among male relatives to over three times this level (M. S. 12.4).

Regarding the subdivision of unipolar affective disorders into the early onset and late onset varieties, we find that although the total morbid risk for affective illness in first degree relatives is somewhat higher in the early onset group (26.3 vs. 18.7), the increased risk for female relatives is evident in both groups. Further, there is no difference in morbid risk for affective illness or alcoholism among the male relatives of both early and late onset probands (14.8 and 13.7 for affective disorders, and 12.4 and 11.3 for alcoholism respectively).

There is, thus no clear evidence to support the subdivision of unipolar depressive illness into the early onset 'depressive spectrum disease', and the late onset 'pure depressive disease' as suggested by Winokur (1975). The late onset unipolar subjects have most of the characteristics of the early onset group but to a milder degree probably reflecting the extent of genetic loading, or a phenotypic variation of the underlying genotype.

On the other hand (Table 7) the fact that a considerable number of first degree relatives of bipolar probands also suffer from a unipolar type of illness, argues against the two types being entirely independent and suggesting the possibility of a common genetic basis for both the unipolar and bipolar types of illnesses.

### Table 7—Type of affective illness among first degree relatives of bipolar probands

|        | Parents no. ill | Sibs. no. ill | Children no. ill | Total ill | BZ     | M.R. |
|--------|-----------------|---------------|------------------|-----------|--------|------|
| Bipolar illness | 5 | 8 | 2 | 15 | 270.5 | 5.5 |
| Unipolar illness | 15 | 21 | 2 | 38 | 270.5 | 14.0 |
| Suicide | 2 | 1 | 0 | 3 | 270.5 | 1.1 |
We shall now attempt to analyse the data presented so far in the light of existing genetic theories, in order to determine the possible mode of transmission in Affective disorders as a whole, and also the unipolar and bipolar groups separately. It has been suggested that affective disorders may have an autosomal dominant pattern of inheritance; in which case all three classes of first degree relatives should show the same risk values. However, as we have seen the risk values vary considerably—being similar for parents and sibs. (19.4 and 22.7) but considerably lower for children (10.9) in the case of bipolar probands. In the unipolar group, the rates for parents and children are similar (20.7 and 19.8 respectively) but considerably higher among the sibs. (27.4).

In the case of recessive inheritance on the other hand, there should be more siblings affected than either parents or children. Although there is evidence of a somewhat increased risk for sibs. of unipolar probands, this does not hold true for the bipolar group.

The third alternative is that of a polygenic model, and the irregular and bilateral distribution of affective illness among both the maternal and paternal relatives supports this possibility, although theoretically, this could also be explained by an autosomal dominant gene of high frequency in the population, but with a low penetrance. There are several methods available for testing the goodness of family data to the additive continuous model of polygenic inheritance, e.g. Falconer (1965), and Slater (1966). In the present study Slater's computational model has been used. This is based on the analysis of ancestral secondary cases (affected ascendant relatives) on the maternal and paternal sides of the family. The relatives were included for study according to the criteria of Slater and Tsuang (1968), & the number of corrected bilateral pairs was calculated according to the following formula:

\[
\text{Number of bilateral pairs} = \frac{2mp}{n-1}, \quad \text{where}
\]

\[m = \text{total secondary cases on maternal side} \]
\[p = \text{total secondary cases on paternal side} \]
\[n = \text{total number of secondary cases.} \]

If polygenic inheritance is involved, one would expect to find approx. twice as many unilateral pairs as bilateral pairs. In the case of a single dominant gene the findings would be significantly different from the expected ratio by a marked excess of unilateral pairs.

Table 8 and 9 give the distribution of secondary cases among the different cate-

| Case No. | Paternal | Maternal | Total | Bilateral pairs (2mp/n-1) |
|----------|----------|----------|-------|-------------------------|
| 6        | 1        | 2        | 3     | 4          | 1        | 2        | 3     | 4          | 2          |
| 22       | 1        | 2        | 1     |            | 1        | 2        | 1     |            | 2          |
| 31       | 1        | 1        | 1     |            | 1        | 2        | 1     |            | 2          |
| 33       | 1        | 1        |       |            | 1        | 2        |       |            | 2          |
| 38       | 1        | 1        |       |            | 1        | 2        |       |            | 2          |
| 40       | 1        | 1        |       |            | 1        | 2        |       |            | 2          |
| 55       | 1        | 1        |       |            | 1        | 3        |       |            | 3          |
| 59       | 1        | 1        |       |            | 1        | 3        |       |            | 3          |
| 63       | 1        | 1        |       |            | 1        | 3        |       |            | 3          |
| 69       | 1        | 1        |       |            | 1        | 3        |       |            | 3          |

Total 6 1 6 3 5 2 4 0 16 11 8.0

1 = parents, 2 = grandparents and their sibs, 3 = uncles and aunts, 4 = cousins.
Table 9—Distribution of affectively ill relatives on paternal and maternal sides in unipolar probands

| Case No. | Paternal | Maternal | Total | Bilateral pairs (2mp/n-l) |
|---------|----------|----------|-------|--------------------------|
|         | 1 2 3 4  | 1 2 3 4  | pat. | mat. |
| 1       | .. .. .. | 1 .. .. | .. 2 |          |
| 5       | 1 1 ..  | 1 .. .. | 2 1  | 2.0 |
| 24      | 1 .. .. | 1 .. .. | 1 2  | 2.0 |
| 45      | .. .. 1 1 | .. .. .. | 2 .. |          |
| 56      | 1 .. .. | 1 .. .. | 1 1  | 2.0 |
| 61      | .. .. .. | 1 .. 1  | .. 3 |          |
| 65      | 1 .. 1  | .. .. .. | 2 2  |        |
| 81      | .. .. .. | .. .. .. | .. 2 |          |
| Total   | 4 1 2 1 5 | 0 5 1 | 8 11 | 6.0 |

1 = parents, 2 = grandparents and their sibs., 3 = uncles and aunts, 4 = cousins.

gories of relatives i.e. (1) parents, (2) grandparents and sibs. of grandparents, (3) uncles and aunts, and (4) cousins, for the bipolar and unipolar groups respectively. Table 10. shows the observed and expected ratio bilateral to unilateral pairs. For the bipolar subjects the difference between the observed and expected ratio is insignificant ($x^2 = 0.158$, df=1, p<0.7). In the case of unipolar subjects also the difference is statistically insignificant ($x^2 = 0.018$, df=1, p> 0.9). These findings strongly suggest the presence of a polygenic pattern of inheritance which is common to all primary affective psychoses (including the unipolar and bipolar types).

In this context we would like to refer back to Table 7 which showed the morbid risk for developing either a bipolar or unipolar illness among the first degree relatives of bipolar probands. The risk for developing a unipolar illness is 1.40 and for bipolar illness 5.5. The fact that unipolar illness is fairly common among the relatives of bipolar probands has been noted previously by James and Chapman (1977) who reported a preponderance of unipolar over bipolar illness by 2:1, the ratio in the present study being 2.5:1. This suggests that the bipolar group is genetically heterogeneous & further, that the bipolar group is genetically heterogeneous and further, that the unipolar and bipolar groups are not completely independent. This heterogeneity has recently been postulated by Mandlewicz et al. (1972) for the bipolar group and by Winokur (1972) for the unipolar group.

It is generally believed that Affective disorders occur more frequently in females than males, the exact ratio among index cases varying considerably depending upon the type of affective illness studied. By and large, the sex ratio approximates 1:1 in the bipolar group, whereas a marked excess of females over males has been reported (by 3:1) in the unipolar group—suggesting that in these cases the transmission may be sex linked (Rosanoff et al., 1935). In the present study also we have found an excess of females in the unipolar probands (67% vs. 23%), whereas males are more than females among the bipolar probands (70% vs. 30%).

Previous family studies have noted that affective illness occurs more frequently among female as compared to male first degree relatives (Winokur and Pitts, 1965; Angst, 1966; Perris, 1968). We have also analysed the morbid risk among male and female relatives of both bipolar and unipolar probands separated by sex of proband. It is seen (Table 5) that among bipolar probands, morbid risk for affective illness is identical for male and female relatives (19.4
TABLE 10—Showing the goodness of fit of observed and expected unilateral and bilateral pairs

|                  | Observed | Expected |
|------------------|----------|----------|
| **A. Bipolar group.** |          |          |
| Unilateral pairs | 19.0     | 18.0     |
| Bilateral pairs  | 8.0      | 9.0      |
| Total            | 27.0     | 27.0     |

$\chi^2 = 0.158, \text{ df}=1, \ p<0.7 \ N.S.$

|                  | Observed | Expected |
|------------------|----------|----------|
| **B. Unipolar group.** |          |          |
| Unilateral pairs | 13.0     | 12.7     |
| Bilateral pairs  | 6.0      | 6.3      |
| Total            | 19.0     | 19.0     |

$\chi^2 = 0.018, \text{ df}=1, \ p>0.9 \ N.S.$

TABLE 11—Morbid risk for affective illness among male and female relatives of unipolar probands separated by sex of proband

|                  | Parents | Siblings | Children | Total |
|------------------|---------|----------|----------|-------|
| **A. Male probands:** |         |          |          |       |
| (i) male relatives | 14.8    | 20.0     | 11.1     | 14.5  |
| (ii) female relatives | 42.0   | 37.7     | 20.0     | 37.6  |
| **B. Female probands:** |         |          |          |       |
| (i) Male relatives | 12.5    | 19.4     | 8.3      | 15.3  |
| (ii) Female       | 14.6    | 33.3     | 30.8     | 27.9  |

TABLE 12—Morbid risk for affective illness among male and female relatives of bipolar probands separated by sex of proband

|                  | Parents | Siblings | Children | Total |
|------------------|---------|----------|----------|-------|
| **A. Male probands:** |         |          |          |       |
| (i) Male relatives | 21.3    | 28.8     | 19.4     | 24.5  |
| (ii) Female relatives | 21.3   | 20.0     | ..       | 17.8  |
| **B. Female probands:** |         |          |          |       |
| (i) Male relatives | 6.5     | 13.6     | ..       | 8.7   |
| (ii) Female       | 22.8    | 23.2     | 25.0     | 23.2  |

and 19.6 respectively); whereas in case of unipolar probands the risk for affective illness among female relatives is double that for male relatives (31.5 vs. 15.0). This is in accordance with the findings of Angst (1966) and Ferris (1968), whereas Winokur et al. (1971, 1975) report an excess of affected female relatives in both the bipolar and unipolar female probands. Further, among the affected relatives of female bipolar probands, they found that affected parents and children show equal proportion
of males and females, but affected sisters are three times more than affected brothers. On the basis of these findings they suggested the possibility of an X linked dominant mode of transmission for the bipolar group. Our data do not support this, since all three categories of relatives i.e. parents, sibs., and children show a higher incidence of female affected relatives.

A further analysis according to sex of probands shows a consistently higher risk for females over males for both male unipolar probands (Table 11)—37.6 vs. 14.5, and also for female unipolar probands—27.9 vs. 15.3. In the case of bipolar probands (Table 12) however, although we still see a marked increase in morbid risk for female relatives of female probands—28.2 vs. 8.7, this is reversed in case of male bipolar probands where more male relatives are affected than females—(17.8 females to 24.5 males).

Table 13 shows the observed and expected male-female sex ratio for affected relatives of male and female probands separately, if we assume the hypothesis of a sex linked dominant mode of inheritance. The observed ratios are seen to be inconsistent with the above hypothesis. Further, we are unable to find any increased risk for female relatives among the total affected relatives of bipolar probands as would be expected in the case of a sex linked dominant trait as postulated by Winokur et al. (1971, 1975). In the case of unipolar group on the other hand, the possibility of a sex linked transmission still remains a possibility with the observed increased risk among female relatives in all three categories of relatives.

In order to investigate this further, we have collected all the affected ‘parent-child’ pairs in both the bipolar and unipolar groups. Included in the pairs are the probands and all first and second degree relatives irrespective of polarity of illness. All doubtful cases or suicides of illness have been excluded (Table 14). In the bipolar group we find that there are 8 father-son pairs (in two of these the mother was also ill, and only one father-daughter pair. There are 7 mother-son and 4 mother-daughter pairs. These findings are against an X linked transmission. In the unipolar group we find only one father-son pair, but in this case the mother was also affectively ill and hence could be a case of mother to son transmission; whereas there are 3 father-daughter pairs. There are 5 mother-son and mother-daughter pairs each. This is clearly compatible with a sex linked transmission in the unipolar group.

### Table 13—Showing sex distribution of affected relatives against hypothesis of sex-link dominance.

|                      | Affected relatives | Expected ratio |
|----------------------|-------------------|----------------|
|                      | Male : female     | Male : female  |
| **Bipolar male probands** |                   |                |
| Parents              | 1 : 1             | 0 : 1          |
| Siblings             | 3 : 2             | 1 : 1          |
| Children             | 19 : 0            | 0 : 1          |
| **Bipolar female probands** |               |                |
| Parents              | 1 : 3             | 1 : 1          |
| Siblings             | 1 : 2             | 1 : 3          |
| Children             | 0 : 25            | 1 : 1          |
| **Unipolar male probands** |                |                |
| Parents              | 1 : 3             | 0 : 1          |
| Siblings             | 1 : 2             | 1 : 1          |
| Children             | 1 : 2             | 0 : 1          |
| **Unipolar female probands** |             |                |
| Parents              | 1 : 1             | 1 : 1          |
| Siblings             | 1 : 2             | 1 : 3          |
| Children             | 1 : 4             | 1 : 1          |

### Table 14—Showing ‘parent-child’ pairs in the bipolar and unipolar groups.

|                    | Bipolar | Unipolar |
|--------------------|---------|----------|
| Father—son         | 8*      | 1*       |
| Father—daughter    | 1       | 3        |
| Mother—son         | 7*      | 5*       |
| Mother—daughter    | 4       | 5        |

*pairs in which both parents were affected.
Assuming this conclusion to be correct, we should be able to verify the following consequences:

(a) Morbid risk for sons and daughters of female probands should be equal.
(b) Male probands should pass the illness to daughters only.
(c) For female probands there should be an excess of ill sisters as compared to brothers.

Except for item (c) above, the other two expectations are not borne out by the data in the present study. What is most striking is the excess of female affected relatives in all categories of relatives for both male and female unipolar probands.

We have previously mentioned the finding of a marked increase in the risk for alcoholism among the male relatives of unipolar probands. In fact the risk for alcoholism is the same as the risk for developing an affective illness among these male relatives (12.4 and 15.0), thus raising the total morbid risk to nearly the same level as for the female relatives. In the bipolar group, however, morbid risk for alcoholism is very low (4.0) and probably not very different from the rate in the general population. It appears therefore, that out of the total affected male relatives of unipolar probands approx. half suffer from an affective illness, while the other half from alcoholism.

It is not possible to arrive at any definite conclusions from the present study. The available evidence supports the contention of their being at least two different forms of Primary Affective Disorders; one would appear to be a more common bipolar type of illness which is essentially polygenic and with equal morbid risk for affective illness in male and female relatives. The other would appear to be a modified expression of the primary manic depressive predisposition due to a dominant X linked that whose manifestation is sex-influenced i.e. it manifests entirely as a depressive illness in females and 50% of the males, while in the other 50% it manifests as alcoholism or sociopathy.

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