Familial Rates of Affective Disorder

A Report From the National Institute of Mental Health Collaborative Study

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- We examined familial rates of affective disorder and related illness in a cohort of 955 probands studied at five centers in the National Institute of Mental Health Collaborative Study of the Psychobiology of Depression: Boston, Chicago, Iowa City, New York, and St. Louis. Six hundred sixteen of these probands were entered into a family study, and 3423 of their first-degree relatives were evaluated. The probands were divided into five diagnostic groups: schizoaffective-bipolar (n = 37), schizoaffective-depressed (n = 18), bipolar I (n = 151), bipolar II (n = 76), and unipolar (n = 330). The relatives of bipolar I probands had a higher rate of bipolar I illness than the relatives of unipolar probands, but the relatives of unipolar probands did not have a higher rate of unipolar illness than the relatives of bipolar I probands. The relatives of probands with schizoaffective disorder, depressed subtype, had a higher rate of schizophrenia than the relatives of schizoaffective-bipolar probands, suggesting that bipolar schizoaffective disorder may be closer to pure affective disorder while schizoaffective depression may be closer to schizophrenia. An increase in bipolar II illness was also observed in the relatives of bipolar II probands. Overall, these data support the widely accepted distinction between bipolar and unipolar affective disorders.

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Although it has been recognized for many years that mental illnesses tend to run in families, only during the past several decades has the examination of familial patterns of affective disorder been a preoccupation of psychiatric research. Interest in this area was triggered by the nearly simultaneous appearance during the 1960s of the work of Perris,13 Angst et al.,14 and Winokur et al.8,9 Although their methods, samples, and definitions varied, each researcher reached similar conclusions: affective disorders tend to be familial, and they should be subdivided into bipolar and unipolar disorders because these two subtypes have different patterns of familial transmission. In general, most subsequent investigations supported these results, although some controversy still exists about the subdivision.9,17

While seminal, this early work was done prior to the development of widely standardized, structured interviews and diagnostic criteria. As a consequence, during the 1970s a group of investigators decided to continue familial studies of affective disorders using standardized methods. A team of investigators from five research centers began to work together toward this goal, leading eventually to the project now called the National Institute of Mental Health (NIMH) Collaborative Study of the Psychobiology of Depression. During its early stages, the project stressed the development of standardized instruments, leading eventually to the development of the Schedule for Affective Disorders and Schizophrenia (SADS),9 the Schedule for Affective Disorders and Schizophrenia—Lifetime Version (SADS-L), Research Diagnostic Criteria (RDC),18 and Family History—Research Diagnostic Criteria (FH-RDC).19 After instrument development and pilot work were completed, a large-scale, multifaceted study was undertaken. The overall goals of this study were to explore and to determine the best methods for classifying and diagnosing the affective disorders, to examine familial patterns of prevalence, to study psychosocial aspects such as personality or life events, and to evaluate long-term course and outcome.

This report focuses on one aspect of the NIMH Collaborative Study, namely, the examination of familial rates of affective disorder. The present report provides an overview of the overall design and methods of this family study and summarizes some of the data collected to date. Other reports will explore genetic models of transmission and the examination of familial patterns of transmission to validate nosology (N. Cox, PhD, T.R., J.R., R. Elston, PhD, J. Schober, MS, unpublished data, 1986).

SUBJECTS AND METHODS

Subjects

The basic design of this study involved ascertaining probands suffering from a wide range of affective disorders: schizoaffective...
disorder (both bipolar and depressive subtypes), bipolar I disorder, bipolar II disorder, and unipolar major depressive disorder (primary and secondary subtypes). A total of 956 probands were considered. From this group, 616 probands were entered into the family study, and their first-degree relatives were interviewed directly if they were available and had consented to the interview. In addition, family-history data were collected for all available first-degree relatives. Among the 956 probands, 13 probands had chronic minor or intermittent depression. Four of these probands were in the family study. Because this sample was too small to analyze, data concerning the probands with chronic minor or intermittent depression are excluded from the remainder of this report.

Centers. The data were collected at five participating centers: Boston (Massachusetts General Hospital and Harvard University), Chicago (Rush-Presbyterian-St Luke’s Medical Center), Iowa City (University of Iowa College of Medicine), New York (New York State Psychiatric Institute and Columbia University), and St Louis (Washington University School of Medicine). Each of these centers contributed samples that differed somewhat diagnostically. Data concerning the samples collected by each of the five centers are shown in Table 1, which breaks down the total sample according to diagnosis of the probands.

Probands. Probands were selected at each of the five centers by drawing from consecutive admissions to the hospital and new evaluations in outpatients. Probands were screened to determine whether they met inclusion criteria for the study. Probands were included if they were white, spoke English as their primary language, were 17 years of age or older, had no evidence of organic mental disorder, had no evidence of mental deficiency (IQ<70), lived in the area (not “transient” or “tourist”), had no obvious terminal illness, and had knowledge of their biologic parents. Furthermore, they were required to meet criteria for one of the inclusion diagnoses for the study. Depending on patient flow, centers took variable numbers of patients: some centers drew from consecutive admissions while others with a larger patient flow selected from admissions at some specified interval (e.g., every 3rd admission). During the first 2 1/2 years of intake, preference was given to probands who were bipolar or had a psychotic affective disorder. During the final year of intake, preference was given to probands suffering from secondary depression. Intake of probands extended over a 9 1/2-year period.

As Table 1 indicates, approximately 80% of the probands were inpatients, while 20% were outpatients. This ratio was distributed more or less evenly across the five centers, with Chicago including slightly more outpatients.

After it was determined that a proband met inclusion criteria, informed consent was obtained and the patient was then interviewed using the SADS. Diagnoses were made using the RDC at the definite level. All sources of information, including medical records, were used. The diagnostic breakdown (made on the basis of lifetime history rather than current episode) for the entire major affective sample is summarized in Table 2. In this sample, 50 probands were schizoaffective-manic (hereafter referred to as schizoaffective-bipolar), 30 probands were schizoaffective-depressed, 186 probands were bipolar I, 112 probands were bipolar II, and 564 probands were unipolar. For the family study, we wished to evaluate all first-degree relatives of at least 600 probands. During the first two years, all probands were asked to consent to participate in the family study. During the third and fourth years, we had nearly achieved this goal, and intake into the family study diminished except for attempts to fill certain potentially diagnostic cells as expediently as possible (e.g., schizoaffective disorder and bipolar disorder). There was no effort to recruit unusually large or informative families, since such an inclusion might have led to an ascertainment bias. There were some center differences in family size, with New York probands tending to have smaller families, while Midwestern probands had larger families.

In this report, probands whose families were evaluated by direct interview are designated as family-study probands, and this sample as a whole is referred to as the family-study sample (n=612). Probands who were not included in the family study are referred to as the nonfamily-study sample (n=339). An overview of the collaborative study sample is provided in Fig 1.

Interviews with the relatives were done only if consent was obtained from the proband. Probands who refused were placed in the nonfamily-study sample. One hundred eighty-three probands, among the total of 339 in the nonfamily-study sample, were refusals. Informed consent was obtained from the relatives as
Table 3.—Sociodemographic Characteristics of the Proband Sample

<table>
<thead>
<tr>
<th>Schizoaffective-Bipolar (n=37)</th>
<th>Schizoaffective-Depressed (n=18)</th>
<th>Bipolar I (n=151)</th>
<th>Bipolar II (n=76)</th>
<th>Unipolar (n=330)</th>
<th>χ² Analysis or F Score</th>
<th>df</th>
<th>p*</th>
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<td>106 (32.2)</td>
<td>16</td>
<td>NS</td>
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<tr>
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<td>52 (35.1)</td>
<td>24 (32.0)</td>
<td>109 (33.3)</td>
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<td>20 (13.5)</td>
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<td></td>
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<td>Mean (SD) age, y</td>
<td>30 (6.4)</td>
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<td>39 (15.2)</td>
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</table>

*NS indicates not significant.
†Based on Hollingshead-Redlich classification.

Fig 1.—Overview of total collaborative study sample. Numbers in parentheses indicate sample sizes when chronic minor or intermittent probands are included.

well. Only relatives 17 years of age or older were interviewed.

The sociodemographic characteristics of the probands in the family-study sample are summarized in Table 3, which divides the probands into five main diagnostic subgroups that are treated hierarchically (see "Data Analysis" section). Among these five groups, there are some differences in marital status and age, but none in sex ratio, religion, or social class.

Relatives.—This report is limited to a discussion of the first-degree relatives (parent, siblings, and children) of the family-study probands. All available relatives for the family-study sample were interviewed using the SADS-L. Diagnoses were made using the RDC. Since all relatives could not be interviewed directly, we also obtained information about them by asking the proband and another family informant about the relative's psychiatric history, using the FH-RDC. In this report, the data based on direct interview with the SADS-L are referred to as family-study data, while the data based on the FH-RDC are referred to as family-history data. Discussion of these data is limited to relatives 17 years of age or older. Within the family-study sample, we have family-study data available for 2226 first-degree relatives and family-history data available for 3423 first-degree relatives. In the nonfamily-study sample, family-history data are available for an additional 1705 relatives. Family-history data for this latter sample were collected using only the proband as an informant. The remainder for this report is limited to a description and analysis of the family-study sample only. In this report, relatives of family-study probands who were evaluated with the SADS-L are referred to as interviewed relatives, while relatives for whom information is limited to family history data are referred to as relatives not interviewed.

The sociodemographic characteristics of the relatives are summarized in Table 4. The relatives do not differ in age or sex ratio, the two major variables that might influence their illness rates. There are some differences in religion and social class.

**Interviewing and Diagnosis**

Interviews of the probands were usually conducted within the first week of entry into the study, and the information on their SADS interviews reflects the severity of symptoms at their worst during the episode, as described by the proband at that time. An intake RDC was completed, reflecting the probands' diagnoses at the time of the intake SADS interview. The probands were followed up closely throughout hospitalization (or during the first two months of outpatient treatment). At the time of discharge (or two months after intake), an update diagnosis was assigned to reflect the most accurate information available (eg, to reflect a change
Table 4.—Sociodemographic Characteristics of Interviewed First-Degree Relatives

<table>
<thead>
<tr>
<th></th>
<th>Schizoaffective-Bipolar</th>
<th>Schizoaffective-Depressed</th>
<th>Bipolar I</th>
<th>Bipolar II</th>
<th>Unipolar</th>
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<td>No. (%) of Relatives</td>
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<td>Women</td>
<td>79 (57.2)</td>
<td>39 (48.1)</td>
<td>323 (56.8)</td>
<td>152 (56.9)</td>
<td>673 (57.5)</td>
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<tr>
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<td>61</td>
<td>569</td>
<td>267</td>
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<td>477</td>
<td>229</td>
<td>1072</td>
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<td>68</td>
<td>477</td>
<td>227</td>
<td>1099</td>
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<td>Mean (SD) for age, y</td>
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<td>43 (17.2)</td>
<td>41 (16.7)</td>
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</table>

*NS indicates not significant.
†Based on Hollingshead-Redlich classification.

from unipolar to bipolar disorder for those patients who developed mania symptoms during the index episode. In the analyses reported herein, the diagnosis reported for the proband is designated as the update diagnosis.

Interviews of the relatives were done by a different group of interviewers who were unaware of the diagnostic status of the proband. All interviews of the relatives were done using the SADS-L. In addition, relatives were evaluated with an interview designed to collect sociodemographic information (the Personal History of Depressive Disorders) and a personality battery. The relatives were scheduled for a face-to-face interview if they lived within a 100-mile radius of the research center (200 miles for the Iowa City center) and could be scheduled for an interview visit. Relatives who did not live within that radius were contacted and interviewed by telephone whenever possible. Approximately 38% of the interviews were done by telephone.

To obtain complete data on all first-degree relatives of the family-study sample, family-history data were collected for all first-degree relatives as well. This information was elicited using a structured interview and predefined diagnostic criteria (FH-RDC). The family-history data were collected from two informants: the proband and one relative designated as the best informant. Best-informant status depended largely on the age of the proband. The best informant was selected by asking the various family members to name the member with the most accurate information about the family as a whole. Information collected from both the proband and the best informant was then reviewed, and a consensus FH-RDC diagnosis using all available information was assigned. All information in this report is based on the consensus FH-RDC diagnosis.

The SADS permits diagnoses to be made at both a definite and a probable level. All SADS diagnoses discussed in this report are at the definite level only. The SADS-L diagnoses are always “probable” by RDC rules, since one less symptom is required for past diagnoses because of difficulties in recall. The major FH-RDC diagnoses are always “definite.” The instrument does permit probable diagnoses to be coded through the use of the nonspecific category other psychiatric disorder for relatives who do not meet the full FH-RDC criteria for a given disorder. As reported elsewhere, examination of the sensitivity and specificity of family-history vs family-study data has suggested that lowering the threshold to this probable level substantially increases the sensitivity of the diagnosis of major depressive disorder. Accordingly, the FH-RDC diagnoses of depression reported herein include other psychiatric disorder—probable depression.

All diagnostic data are organized in a single file, the pedigree file. In this file, each family is treated as a unit, and family-history and family-study data are summarized together. A sample pedigree, coded for data entry into the pedigree file, appears in Fig 2. As Fig 2 indicates, both family-history and family-study data are available for many first-degree relatives. In each center, therefore, a senior and experienced member of the project was responsible for reviewing family-history and family-study diagnoses and assigning a clinical consensus diagnosis to summarize all information available and to reflect overall clinical judgment. The guidelines for this procedure were included in a procedure manual used in all
centers. In general, direct interview data were given a stronger weight than family-history data in making consensus diagnoses. In some instances, however, evidence appeared to suggest that the family member had forgotten or had chosen to minimize past symptoms; in these cases, greater weight was given to the family-history data. For those relatives who were not directly interviewed, only family-history data provided the basis for the consensus diagnosis. The SADS, SADS-L, RDC, and FH-RDC all permit multiple overlapping diagnoses. Therefore, in this study a particular proband or relative may have two or three different diagnoses that may occur at the same time or at different periods (eg, major depression, alcoholism, and schizotypal personality). Because the data set includes information about age of onset for each disorder, the longitudinal evolution of psychopathology can be examined.

Training and Reliability

Careful attention was given to training and reliability in the study. The interviewers came from a broad range of backgrounds, including psychiatrists, psychologists with PhDs, and individuals with master's and bachelor's level training in fields such as psychology and social work. We have previously examined the effects of past educational background on interviewing and diagnostic habits. Our results suggest that, when standardized training has been provided, raters from a variety of backgrounds do not differ significantly in their diagnostic interviewing habits.26

Case narratives and training tapes were developed for use in this study. All interviewers went through a carefully supervised two-month training period. In addition, regular training meetings were held for all raters from the five centers to update training, to compare interviewing and diagnostic habits, and to minimize interviewer "drift." Careful attention was also given to achieving reliability of both symptom ratings and diagnoses. A series of reliability studies has been conducted and reported elsewhere.27-32 An initial pilot study was done of the SADS, SADS-L, and RDC to document that adequate interrater reliability could be achieved in each of the five centers. Subsequently, we turned our attention to cross-center reliability and conducted both test-retest and interrater reliability studies using raters from all five centers to examine whether diagnostic behavior differed in each of the five centers. In general, the results of these studies suggest that good intercenter and intracenter reliability had been achieved.

Data Analysis

For the present report, the affective diagnoses of all relatives and probands have been treated hierarchically. As described earlier in this report, the SADS, SADS-L, RDC, and FH-RDC are nonhierarchical on a lifetime basis; they permit the interviewer to make multiple diagnoses. Thus, a proband may have been diagnosed as having a manic disorder for the current episode but may have had a past history of schizoaffective disorder, manic type. In this report, all affective diagnostic information has been summarized in a single diagnosis so that the most severe lifetime diagnosis has been assigned to each relative and proband; therefore, each proband has only one nonoverlapping affective diagnosis. The order of the hierarchy is as follows: schizoaffective disorder, bipolar type; schizoaffective disorder, depressed type; bipolar I disorder; bipolar II disorder; and unipolar major depressive disorder. Relatives with manic disorder only were included in the bipolar I group, and relatives with hypomanic disorder only were classified in the bipolar II group. The SADS/SADS-L system also permits diagnoses of minor or intermittent disorders, which were treated as lower in the hierarchy. Cyclothymic personality is reported both hierarchically and nonhierarchically. In addition, other nonaffective diagnoses were available, such as alcoholism, drug abuse, or antisocial personality. In this report, these diag-
Table 5.—Comparison of Rates of Illness in Interviewed Relatives

<table>
<thead>
<tr>
<th>Diagnosis in Relatives</th>
<th>Schizoaffective-Bipolar Probands (n = 138)</th>
<th>Schizoaffective-Depressed Probands (n = 81)</th>
<th>Bipolar I Probands (n = 569)</th>
<th>Bipolar II Probands (n = 267)</th>
<th>Unipolar Probands (n = 1171)</th>
<th>( \chi^2 ) Analysis†</th>
<th>( P^* )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hierarchical</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>1 (0.7)</td>
<td>2 (2.5)</td>
<td>6 (1.0)</td>
<td>1 (0.4)</td>
<td>3 (0.3)</td>
<td>†</td>
<td>0.377</td>
</tr>
<tr>
<td>Schizoaffective-bipolar</td>
<td>1 (0.7)</td>
<td>0</td>
<td>3 (0.5)</td>
<td>1 (0.4)</td>
<td>2 (0.2)</td>
<td>†</td>
<td>NS</td>
</tr>
<tr>
<td>Both poles</td>
<td>0</td>
<td>0</td>
<td>2 (0.3)</td>
<td>0</td>
<td>1 (0.1)</td>
<td>†</td>
<td>NS</td>
</tr>
<tr>
<td>Manic only</td>
<td>1 (0.7)</td>
<td>0</td>
<td>1 (0.2)</td>
<td>1 (0.4)</td>
<td>1 (0.1)</td>
<td>†</td>
<td>NS</td>
</tr>
<tr>
<td>Schizoaffective-depressed</td>
<td>0</td>
<td>0</td>
<td>1 (0.2)</td>
<td>0</td>
<td>4 (0.3)</td>
<td>†</td>
<td>NS</td>
</tr>
<tr>
<td>Bipolar I</td>
<td>5 (3.6)</td>
<td>0</td>
<td>22 (3.9)</td>
<td>3 (1.1)</td>
<td>7 (0.6)</td>
<td>†</td>
<td>29.882†</td>
</tr>
<tr>
<td>Bipolar II</td>
<td>8 (5.6)</td>
<td>3 (3.7)</td>
<td>24 (4.2)</td>
<td>22 (8.2)</td>
<td>34 (2.9)</td>
<td>†</td>
<td>17.011†</td>
</tr>
<tr>
<td>Unipolar</td>
<td>35 (25.4)</td>
<td>17 (21.0)</td>
<td>130 (22.8)</td>
<td>70 (26.2)</td>
<td>333 (28.4)</td>
<td></td>
<td>7.505</td>
</tr>
<tr>
<td>Primary</td>
<td>24 (17.4)</td>
<td>12 (16.0)</td>
<td>100 (17.6)</td>
<td>49 (18.3)</td>
<td>245 (20.9)</td>
<td></td>
<td>4.077</td>
</tr>
<tr>
<td>Secondary</td>
<td>9 (6.5)</td>
<td>2 (2.5)</td>
<td>25 (4.4)</td>
<td>15 (5.6)</td>
<td>75 (6.4)</td>
<td>†</td>
<td>4.862†</td>
</tr>
<tr>
<td>Cyclothymic personality</td>
<td>0</td>
<td>0</td>
<td>1 (0.2)</td>
<td>1 (0.4)</td>
<td>3 (0.3)</td>
<td>†</td>
<td>NS</td>
</tr>
<tr>
<td>Minor or intermittent depressed</td>
<td>8 (5.8)</td>
<td>8 (9.9)</td>
<td>38 (6.7)</td>
<td>22 (8.2)</td>
<td>106 (9.0)</td>
<td>†</td>
<td>4.251†</td>
</tr>
<tr>
<td>Nonhierarchical</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cyclothymic personality</td>
<td>3 (2.2)</td>
<td>0</td>
<td>4 (0.7)</td>
<td>7 (2.6)</td>
<td>14 (1.2)</td>
<td>†</td>
<td>NS</td>
</tr>
<tr>
<td>Alcoholism</td>
<td>20 (21.0)</td>
<td>12 (14.8)</td>
<td>71 (12.5)</td>
<td>37 (13.9)</td>
<td>176 (15.0)</td>
<td>†</td>
<td>6.903†</td>
</tr>
<tr>
<td>Drug abuse</td>
<td>8 (5.8)</td>
<td>2 (2.5)</td>
<td>27 (4.7)</td>
<td>15 (5.6)</td>
<td>68 (5.8)</td>
<td>†</td>
<td>2.290†</td>
</tr>
<tr>
<td>Antisocial personality disorder</td>
<td>4 (2.8)</td>
<td>0</td>
<td>1 (0.2)</td>
<td>2 (0.7)</td>
<td>11 (0.9)</td>
<td>†</td>
<td>0.392†</td>
</tr>
<tr>
<td>Brieu's syndrome</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2 (0.2)</td>
<td>†</td>
<td>NS</td>
</tr>
<tr>
<td>Generalized anxiety disorder</td>
<td>11 (8.0)</td>
<td>3 (3.7)</td>
<td>37 (6.5)</td>
<td>19 (7.1)</td>
<td>93 (7.9)</td>
<td>†</td>
<td>2.891†</td>
</tr>
<tr>
<td>Phobic disorder</td>
<td>9 (6.5)</td>
<td>2 (2.5)</td>
<td>10 (1.8)</td>
<td>12 (4.5)</td>
<td>54 (4.6)</td>
<td>†</td>
<td>11.751†</td>
</tr>
<tr>
<td>Panic disorder</td>
<td>3 (2.2)</td>
<td>1 (1.2)</td>
<td>6 (1.0)</td>
<td>2 (0.7)</td>
<td>20 (1.7)</td>
<td>†</td>
<td>0.193</td>
</tr>
<tr>
<td>Obsessive-compulsive disorder</td>
<td>3 (2.2)</td>
<td>0</td>
<td>3 (0.5)</td>
<td>3 (1.1)</td>
<td>4 (0.3)</td>
<td>†</td>
<td>NS</td>
</tr>
<tr>
<td>Unspecified functional psychosis</td>
<td>0</td>
<td>0</td>
<td>3 (0.5)</td>
<td>0</td>
<td>0</td>
<td>†</td>
<td>NS</td>
</tr>
<tr>
<td>None of the above</td>
<td>59 (42.7)</td>
<td>44 (54.3)</td>
<td>302 (53.1)</td>
<td>120 (45.0)</td>
<td>539 (46.0)</td>
<td>†</td>
<td>11.481†</td>
</tr>
<tr>
<td>Never mentally ill</td>
<td>56 (40.6)</td>
<td>40 (49.4)</td>
<td>258 (45.3)</td>
<td>105 (39.3)</td>
<td>476 (40.6)</td>
<td>†</td>
<td>6.198</td>
</tr>
</tbody>
</table>

*NS indicates not significant.
† All \( \chi^2 \) tests have 4 df.
‡ Fisher's exact test.

Table 6.—Comparison of Rates of Illness for All Relatives by Family History

<table>
<thead>
<tr>
<th>Diagnosis in Relatives</th>
<th>Schizoaffective-Bipolar Probands (n = 179)</th>
<th>Schizoaffective-Depressed Probands (n = 113)</th>
<th>Bipolar I Probands (n = 867)</th>
<th>Bipolar II Probands (n = 392)</th>
<th>Unipolar Probands (n = 1872)</th>
<th>( \chi^2 ) Analysis†</th>
<th>( P^* )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hierarchical</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>3 (1.7)</td>
<td>1 (0.9)</td>
<td>6 (0.7)</td>
<td>3 (0.8)</td>
<td>4 (0.2)</td>
<td>†</td>
<td>.0193</td>
</tr>
<tr>
<td>Psychosis</td>
<td>5 (2.8)</td>
<td>2 (1.8)</td>
<td>17 (2.0)</td>
<td>4 (1.0)</td>
<td>18 (1.0)</td>
<td>†</td>
<td>7.853</td>
</tr>
<tr>
<td>Schizoaffective-bipolar</td>
<td>0</td>
<td>0</td>
<td>3 (0.3)</td>
<td>0</td>
<td>2 (0.1)</td>
<td>†</td>
<td>NS</td>
</tr>
<tr>
<td>Both poles</td>
<td>0</td>
<td>0</td>
<td>1 (0.1)</td>
<td>0</td>
<td>1 (0.1)</td>
<td>†</td>
<td>NS</td>
</tr>
<tr>
<td>Manic only</td>
<td>1 (0.6)</td>
<td>0</td>
<td>4 (0.5)</td>
<td>0</td>
<td>9 (0.5)</td>
<td>†</td>
<td>NS</td>
</tr>
<tr>
<td>Schizoaffective-depressed</td>
<td>0</td>
<td>0</td>
<td>4 (0.5)</td>
<td>0</td>
<td>3 (0.2)</td>
<td>†</td>
<td>NS</td>
</tr>
<tr>
<td>Bipolar I</td>
<td>5 (2.8)</td>
<td>2 (1.8)</td>
<td>50 (5.8)</td>
<td>11 (2.9)</td>
<td>12 (0.6)</td>
<td>†</td>
<td>68.979†</td>
</tr>
<tr>
<td>Unipolar</td>
<td>40 (22.3)</td>
<td>20 (17.8)</td>
<td>192 (22.3)</td>
<td>121 (30.9)</td>
<td>481 (25.7)</td>
<td>†</td>
<td>15.041†</td>
</tr>
<tr>
<td>Nonhierarchical</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcoholism</td>
<td>38 (21.2)</td>
<td>16 (14.2)</td>
<td>131 (15.1)</td>
<td>54 (13.8)</td>
<td>280 (15.0)</td>
<td></td>
<td>5.859†</td>
</tr>
<tr>
<td>Drug abuse</td>
<td>12 (6.7)</td>
<td>2 (1.8)</td>
<td>39 (4.5)</td>
<td>21 (5.4)</td>
<td>70 (3.7)</td>
<td>†</td>
<td>6.920†</td>
</tr>
<tr>
<td>Antisocial personality disorder</td>
<td>8 (4.5)</td>
<td>4 (3.5)</td>
<td>23 (2.6)</td>
<td>27 (6.9)</td>
<td>68 (3.6)</td>
<td>†</td>
<td>13.736†</td>
</tr>
<tr>
<td>Unspecified functional psychosis</td>
<td>2 (1.1)</td>
<td>0</td>
<td>12 (1.4)</td>
<td>3 (0.8)</td>
<td>9 (0.4)</td>
<td>†</td>
<td>NS</td>
</tr>
<tr>
<td>Never mentally ill</td>
<td>94 (52.5)</td>
<td>68 (60.2)</td>
<td>443 (51.1)</td>
<td>174 (44.4)</td>
<td>985 (52.5)</td>
<td>†</td>
<td>12.410†</td>
</tr>
</tbody>
</table>

*NS indicates not significant.
† All \( \chi^2 \) tests have 4 df.
‡ Fisher's exact test.
Table 7.—Rates of RDC vs More Strictly Defined Unipolar Depression in Interviewed First-Degree Relatives*  

<table>
<thead>
<tr>
<th>Definition Used in Relatives</th>
<th>Schizoaffective-Bipolar Probands (n = 138)</th>
<th>Schizoaffective-Depressed Probands (n = 81)</th>
<th>Bipolar I Probands (n = 569)</th>
<th>Bipolar II Probands (n = 267)</th>
<th>Unipolar Probands (n = 1171)</th>
<th>χ² Analysis†</th>
<th>P</th>
<th>Unipolar: Bipolar</th>
</tr>
</thead>
<tbody>
<tr>
<td>RDC-defined</td>
<td>35 (25.5)</td>
<td>17 (21.0)</td>
<td>130 (22.8)</td>
<td>70 (26.2)</td>
<td>333 (28.4)</td>
<td>7.505</td>
<td>NS</td>
<td>1.2</td>
</tr>
<tr>
<td>Illness &lt; 1 mo</td>
<td>31 (22.5)</td>
<td>14 (17.3)</td>
<td>107 (19.8)</td>
<td>60 (22.5)</td>
<td>274 (23.4)</td>
<td>5.618</td>
<td>NS</td>
<td>1.2</td>
</tr>
<tr>
<td>Incapacitated</td>
<td>2 (1.4)</td>
<td>3 (3.7)</td>
<td>10 (1.8)</td>
<td>11 (4.1)</td>
<td>31 (2.6)</td>
<td>5.215</td>
<td>NS</td>
<td>1.4</td>
</tr>
<tr>
<td>Psychotic</td>
<td>1 (0.7)</td>
<td>0</td>
<td>3 (0.5)</td>
<td>5 (1.9)</td>
<td>6 (0.5)</td>
<td>†</td>
<td>NS</td>
<td>1.0</td>
</tr>
<tr>
<td>Recurrent</td>
<td>16 (11.6)</td>
<td>10 (12.3)</td>
<td>48 (8.4)</td>
<td>33 (12.4)</td>
<td>127 (10.8)</td>
<td>4.176</td>
<td>NS</td>
<td>1.3</td>
</tr>
<tr>
<td>Somatically treated§</td>
<td>16 (11.6)</td>
<td>8 (9.9)</td>
<td>48 (8.4)</td>
<td>38 (12.4)</td>
<td>168 (14.3)</td>
<td>13.600</td>
<td>.0087</td>
<td>1.7</td>
</tr>
<tr>
<td>Hospitalized</td>
<td>4 (2.9)</td>
<td>1 (1.2)</td>
<td>19 (3.3)</td>
<td>15 (5.5)</td>
<td>65 (5.5)</td>
<td>7.960</td>
<td>.0031</td>
<td>1.7</td>
</tr>
</tbody>
</table>

*NS indicates not significant; RDC, Research Diagnostic Criteria.  
†All χ² tests have 4 df.  
§Treatment with drugs, electroconvulsive therapy, or both.

noises are treated nonhierarchically, so that multiple diagnoses from this nonaffective group have been assigned for some probands and relatives.

Because affective disorders can occur for the first time in midlife or later in life, and because first-degree relatives usually have a broad age range and include many relatively young individuals who have not passed through the age of risk, family data are often reported with an age correction referred to as morbidity risk. This correction indicates the expected lifetime prevalence if all first-degree relatives had actually passed through the age of risk.

In the present report, we elected not to calculate morbidity risk for several different reasons. First, examination of the age of onset data in our sample has suggested an age-period cohort effect with the age of onset steadily decreasing in the younger first-degree relatives. This effect may lead to erroneously high estimates of morbidity risk. Second, we examined the mean ages and age distributions across the relatives in each of the five hierarchical subsamples and found that they did not differ significantly from one another. There were no differences among the five groups of relatives could not be explained on the basis of different age structures within these groups. For these reasons, we have elected to report our data in terms of actual raw numbers and percentages. Because of the large scale of the present investigation, we regard it as archival. Providing subsequent investigators with these raw numbers will permit them to apply other estimates and calculations as they choose to make cross-study comparisons.

Estimates of lifetime prevalence can also be affected by sex ratio since, in general, women have a higher rate of affective disorder than men. We also compared the sex ratio of the five subsamples and found that it did not differ among the groups. Some preliminary reports of subjects of this data set have been previously published.27

**RESULTS**

Table 5 summarizes the rates of illness observed in the interviewed first-degree relatives. Diagnosis in both probands and relatives is hierarchical. The diagnosis of the proband appears at the top of each column. The relatives are divided into five major groups: relatives of schizoaffective-bipolar probands (n = 138), relatives of schizoaffective-depressed probands (n = 81), relatives of bipolar I probands (n = 569), relatives of bipolar II probands (n = 267), and relatives of unipolar probands (n = 1171). These relatives differ in one another in their rates of two illnesses: bipolar I disorder and bipolar II disorder. The relatives of schizoaffective-bipolar probands and bipolar I probands both have a high rate of bipolar I disorder. The relatives of bipolar II probands have a high rate of bipolar II disorder. While the relatives of unipolar probands have a somewhat higher rate of unipolar disorder, the difference is not statistically significant (P < .1). There are no differences among the groups of relatives in rates of "affective spectrum" diagnoses, such as cyclothymic personality or chronic intermittent depression. The groups also show some modest differences in rates of other diagnoses. The relatives of schizoaffective-bipolar probands, bipolar II probands, and unipolar probands have significantly increased rates of phobic disorder.

Table 6 makes similar comparisons for a somewhat larger sample of first-degree relatives, namely, those for whom we have family-history data. In contrast to Table 5, which was based on direct interview (SADS-L) diagnoses, the data in Table 6 are based only on family-history (FH-RDC) diagnoses. We have reported elsewhere on the sensitivity and specificity of the family-history method.28 In general, sensitivity is markedly reduced when diagnoses are made from family history alone, and interview data are usually considered to be more accurate. Nevertheless, familial patterns of illness are often studied using family-history data only, and our family-history data are summarized to permit comparison with other investigations employing the family-history method.

As Table 6 indicates, the results based on the family-history method differed somewhat from those based on the family-study method. Relatives of bipolar I probands continue to have a significantly higher rate of bipolar I illness. Some differences are also observed in the rate of unipolar depression, with the relatives of bipolar II probands having higher rates than those reported in the other groups. Differences among the five groups of relatives are observed in the rate of unipolar depression, with higher rates of unipolar depression being observed in the relatives of bipolar II probands. While the detailed analyses differ somewhat from those based on the family-study data, the overall direction of the findings is similar. That is, data in both tables suggest that bipolar I disorder tends to be more common. Because the diagnosis of bipolar II disorder is not made in relatives using family-history data, one cannot determine whether bipolar II probands have a higher rate of bipolar II disorder in their relatives; however, these probands do (somewhat surprisingly) exhibit an increased rate of unipolar depression.

**COMMENT**

Many previous studies have reported that the relatives of bipolar I probands tend to have a higher rate of bipolar I illness compared with relatives of unipolar probands, while the relatives of unipolar probands tend to have a higher rate of unipolar illness compared with relatives of bipolar probands. While this investigation confirms the former finding, it does not confirm the latter. Furthermore, our observed rates of depression are substantially higher than those reported in other studies. Consequently, we were interested in learning whether our findings might be explained by some methodological differences.

One possible explanation for these findings is a difference in case definition. Some investigators (e.g., Perris29) have used an extremely stringent definition for unipolar depres-
sion, requiring the presence of three recurrent unipolar episodes. On the other hand, the RDC definition of depression is relatively broad, requiring only the presence of some type of dysphoric mood and four other depressive symptoms for at least two weeks for a current diagnosis and only three symptoms in one week for a past diagnosis. Table 7 examines the effect of applying more stringent case definitions to the concept of unipolar depression. This table shows data only for the rate of depression in first-degree relatives for each of the five groups of probands (schizoaffective-bipolar, schizoaffective-depressed, bipolar I, bipolar II, and unipolar). The RDC definition is the broadest. Increasing restrictions are added to the definition by requiring (1) the presence of symptoms for one month or more, as specified in the St Louis criteria; (2) incapacity; (3) the presence of psychotic symptoms; (4) the presence of at least two episodes; (5) the prescription of some type of somatic therapy; or (6) hospitalization for an affective episode.

As Table 7 indicates, rates of depression do not differ among the five groups of relatives using the broader case definition, but they do differ when the definitions become more restrictive. The relative increase in unipolar depression among the relatives of unipolar patients, so frequently observed in previous studies, can be observed in the present study when one limits the definition of depression in first-degree relatives to those who have received somatic therapy or who have been hospitalized. In either case, the rate of unipolar depression is 1.7 times as common in the relatives of unipolar probands as it is in the relatives of bipolar I probands. Somewhat surprisingly, however, rates of depression are also relatively high among the relatives of both bipolar II and schizoaffective-bipolar probands, using the restrictive definition of somatically treated, and they are also relatively high in the relatives of bipolar II probands when the requirement of hospitalization is added.

Since most previous investigators have reported rates of illness in relatives of affectively disordered probands as morbid risk, the rates described in the present study are not directly comparable with those of prior studies. It is clear, however, that our rates of major depression are somewhat higher than those previously reported. For relatives of bipolar probands, morbid risk estimates for rates of depression have ranged from a low of 0.5% in the work of Perris et al.20 to a high of 22.4% in the work of Mendlewicz and Ranier.21 These rates have been well reviewed in a recent article by Gershon et al.22 who cite 10.2% as the average rate of unipolar depression among the relatives of bipolar patients, while the average among relatives of unipolar patients is 6.5%. Perhaps the studies most comparable to the present one are the works completed by Weissman et al.17,23 in which SADS interviews and RDC criteria with some modification were used. They report a morbid risk for major depression of 9.5% among the relatives of bipolar patients and 10.4% among the relatives of severely affected unipolar patients studied at the NIMH site, while the rates at the Yale University site (New Haven, Conn) were 16.0 for the relatives of severely affected probands and 14.3 for the relatives of mildly affected probands. They narrowed the RDC definition by requiring four weeks of illness and impairment or incapacitation of functioning in the major social role. Requiring the persistence of symptoms for at least a month brings our rates somewhat closer to theirs, although they still remain substantially higher. Some of these differences may be accounted for by differences in sampling. For example, our relatives appeared to be substantially younger than those in the Weissman et al.24 study. Since we have observed that rates of depression appear to be increasing in younger individuals, some of the differences may be explained by the fact that we have sampled more members from more frequently affected younger cohorts.

The strongest evidence to emerge from the present study is the relative increase of bipolar I disorder among the relatives of probands suffering from bipolar I disorder. This finding is consistently replicated in both the data based on direct interview and in the family-history data. Bipolar I disorders seldom occur in the relatives of unipolar probands.

Bipolar I disorder is also relatively common in the relatives of schizoaffective-bipolar probands. This finding is quite strong in the family-study data and also emerges from the family-history data. On the other hand, schizophrenia is relatively uncommon among the relatives of schizoaffective-bipolar patients. These results are consistent with the possibility that schizoaffective-bipolar disorder is more closely related to bipolar affective disorder than it is to schizophrenia. On the other hand, the relatives of probands suffering from schizoaffective disorder with depressive features only have a relatively higher rate of schizophrenia and a zero prevalence of bipolar I disorder, suggesting that schizoaffective depression may be more closely related to schizophrenia.27

The results of this study provide some partial support for the independence of bipolar II disorder.26,27,28 Bipolar II illness is substantially increased among the relatives of bipolar II probands, suggesting that this disorder may to some extent breed true. Only 11.6% of the relatives of bipolar II probands have bipolar I disorder, while 8.2% have bipolar I disorder.

Overall, these data provide partial support for the widely accepted distinction between bipolar and unipolar affective disorders. These results suggest that bipolar I and bipolar II disorders may be nosologically and genetically distinct from each other and from unipolar disorder, but they do not demonstrate this conclusively because of the similarity in rates of unipolar illness in all three groups. The aforementioned results indicate that schizoaffective-bipolar disorder may be related to bipolar I disorder. On the other hand, no clear patterns of inheritance are noted in the relatives of unipolar or schizoaffective-depressed patients. Consequently, the nosological and genetic status of these disorders remains unclear, although more complex genetic analyses may clarify some of these issues.

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References


Familial Rates—Andreasen et al


