Depressives with Secondary Alcoholism: Psychiatric Disorders in Offspring*

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ABSTRACT. The risk of psychiatric illness among the offspring of probands with major depression and secondary alcoholism was examined. The offspring aged 6-17 (N = 107) and 18 + (N = 171) of probands with major depression (114 with depression only and 19 with secondary alcoholism) were compared with the offspring aged 6-17 (N = 87) and 18 + (N = 103) of controls (N = 82). Offspring of probands with secondary alcoholism had a threefold greater risk of alcoholism and a fivefold greater risk of antisocial personality-conduct disorder compared with offspring of probands with depression only, and a threefold greater risk of alcoholism and a 20-fold greater risk of antisocial personality-conduct disorder compared with offspring of controls. Familial aggregation of alcoholism was observed only among probands with secondary alcoholism. The presence of secondary alcoholism in depressed probands did not convey additional increase in risk of either major depression or anxiety disorders to offspring beyond that observed among offspring of probands with depression only. This suggests that depression and alcoholism are not alternate forms of expression of the same underlying illness. Assortative mating for alcoholism among parents was related to increased risk of both alcoholism and antisocial personality-conduct disorder but not of major depression among offspring. A linear effect on rates of these disorders according to the number of parents with alcoholism was observed. (J. Stud. Alcohol 46: 199-204, 1985)

FAMILIAL AGGREGATION of both major depression and alcoholism has been frequently noted (Gershon et al., 1976; Goodwin, 1983). Twin and cross-fostering studies have established that genetic factors contribute to the development of both disorders (Goodwin et al., 1973; Kidd and Weissman, 1978). Although the discordance in genetically similar individuals also suggests the importance of environmental contributions, no specific environmental factors have consistently been identified for either disorder (Goodwin, 1983; Hirschfeld and Cross, 1982).

The clustering of depression, alcoholism and antisocial personality within individuals and families has also been frequently observed (Lewis et al., 1983; Pitts and Winokur, 1966; Schuckit, 1979; Winokur, 1979). Despite this clustering, the independence of transmission of these disorders has been demonstrated in several studies (Angst, 1966; Cloninger and Reich, 1983; Cloninger et al., 1979; Merikangas et al., in press). Thus, the observed association between these disorders can be attributed to nontransmissible, random environmental factors that tend to cluster in families (Cloninger et al., 1979). It is also likely that there is a synergistic effect of developing a second illness in the presence of a primary psychiatric illness.

Because of the familial nature of both alcoholism and depression, offspring of probands with either disorder have been identified (Tarter, 1983) to be at high risk for developing these illnesses. Children of depressed parents have been found (Beardslee et al., 1983; Connors et al., 1980) to have increased rates of psychopathology in general and affective symptoms in particular. Children of alcoholics have a fourfold increase in the risk of developing alcoholism, and an association between childhood conduct disorders and adult alcoholism has been demonstrated in several studies (e.g., Cadoret and Gath, 1978; Goodwin et al., 1975). Several studies of children of probands with depression and probands with alcoholism are currently in progress.

The present study compared the rates of psychiatric illness among the offspring of probands with major depression and controls in the Yale Family-Genetic Study of Depression. Weissman et al. (1984b) reported that more children of the depressed probands than of the control probands had symptoms, psychological treatment and DSM-III (American Psychiatric Association,
Previous analyses of these data (Leckman et al., 1983; Merikangas et al., in press) have also shown that secondary diagnoses in probands convey additional risk of psychiatric illness to their adult first-degree relatives. Furthermore, specificity of transmission has been observed (Weissman et al., 1984a) for depression and anxiety disorders in the children aged 6-17 of probands with these disorders. This article will focus on the risk of depression and alcoholism in the offspring of depressed probands with secondary alcoholism.

Method

Probands

There were 133 patients at the Yale University Depression Research Unit or other facilities in the Department of Psychiatry with major depression defined according to modified Research Diagnostic Criteria (RDC) (Spitzer et al., 1978). Probands were divided into the mildly depressed (N = 89) and the severely depressed (N = 44), based on their history of hospitalization. The severely depressed probands had a history of hospitalization for depression whereas the mildly depressed had received outpatient treatment only.

Because this original severity distinction did not discriminate rates among relatives, the two groups of depressed probands have been collapsed in the analyses of these data. For these analyses, the depressed probands were classified according to the presence or absence of alcoholism. In all of the probands with alcoholism, the onset of depression preceded the onset of alcoholism. All probands with primary alcoholism or antisocial personality were excluded from the study.

The 82 controls, who were obtained from the community survey of Weissman and Myers (1978), had no history of psychiatric illness. The probands were all White and were group-matched by sex and age. Complete pedigrees for each proband were systematically obtained and diagnostic assessments were made according to RDC for every living or dead first-degree relative.

Adult first-degree relatives

There was a total of 1331 adult first-degree relatives. Direct interviews, using a modified Schedule for Affective Disorders and Schizophrenia (SADS) (Endicott and Spitzer, 1978), were obtained from adult relatives whenever possible. If not, family history data were obtained from multiple informants and from medical records. Direct interviews were conducted with 40% of the relatives and family history information was available from multiple informants for over 55%. Diagnostic assessments of the relatives were made blindly with respect to the status of the proband, using a best estimate procedure (Leckman et al., 1982). Diagnoses of adult relatives were made according to modified RDC and were based on all available information.

Children aged 6-17

Data were also collected on the children aged 6-17 of the probands. One hundred of the 215 probands in the study had children in this age group; there was a total of 194 children at risk. Children aged 18 and under were not interviewed directly. Instead, information on minor children was obtained by family history from the proband, spouse and other first-degree relatives.

A screening instrument administered to the proband, spouse and all first-degree relatives determined symptoms of psychopathology, behavioral problems and psychological treatment in any of their children aged 6-17 at the time of the proband interview. First there was a general probe about problems with the child and then a symptom list was read to the informant. Information was obtained separately for each child. Children under the age of 6 were excluded from such assessments because the instruments were inappropriate for that age group. When there were positive answers to symptoms, the interviewers were instructed to code them and to record details in a narrative form as well. The interviewers collecting the symptom data were not blind with respect to the status of the proband but were blind to the status of the spouse and other informants. Concordance between parents' reports was assessed when both were available—in general, there was quite high agreement.

A best estimate diagnosis based on DSM-III criteria was made by a psychiatrist with clinical and research training in child psychiatry who was not involved in the original data collection and who was blind to the clinical status of the proband. All available information on the child from parents' reports and medical records was reviewed in part of the diagnostic process.

Results

The number of probands and offspring by the presence of depression and alcoholism in the proband is presented in Table 1. Offspring aged 18+ were first examined separately from those aged 6-17 because of the differences in methodology for ascertaining psychopathology in the two groups. The percentages of diagnoses in offspring by the presence of depression and alcoholism in the proband are shown in Table 2. The rates of major depression, anxiety disorders and antisocial personality are higher among offspring over age 18 of probands with depression alone than among offspring of controls. The rates of alcoholism were

<table>
<thead>
<tr>
<th>Table 1. Number of probands and offspring by the presence of primary depression and secondary alcoholism in the proband</th>
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<tbody>
<tr>
<td></td>
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<td>------------------</td>
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<tr>
<td><strong>Probands</strong></td>
</tr>
<tr>
<td><strong>Offspring</strong></td>
</tr>
<tr>
<td>Aged 6-17</td>
</tr>
<tr>
<td>Aged 18+</td>
</tr>
</tbody>
</table>
TABLE 2. Percentage of diagnoses in offspring by the presence of depression and alcoholism in the proband

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Depression alone</th>
<th>Depression and alcoholism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Offspring aged 18+</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N at risk (103)</td>
<td>(103)</td>
<td>(148)</td>
<td>(23)</td>
</tr>
<tr>
<td>Major depression</td>
<td>6.8</td>
<td>14.9</td>
<td>13.0</td>
</tr>
<tr>
<td>Alcoholism</td>
<td>16.5</td>
<td>12.2</td>
<td>34.8</td>
</tr>
<tr>
<td>Any anxiety</td>
<td>9.7</td>
<td>19.6</td>
<td>21.7</td>
</tr>
<tr>
<td>Antisocial personality</td>
<td>1.9</td>
<td>6.1</td>
<td>30.4</td>
</tr>
<tr>
<td>Offspring aged 6-17</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N at risk (87)</td>
<td>(87)</td>
<td>(93)</td>
<td>(14)</td>
</tr>
<tr>
<td>Major depression</td>
<td>0.0</td>
<td>12.9</td>
<td>14.3</td>
</tr>
<tr>
<td>Alcoholism</td>
<td>0.0</td>
<td>1.1</td>
<td>7.1</td>
</tr>
<tr>
<td>Any anxiety</td>
<td>2.3</td>
<td>9.7</td>
<td>14.3</td>
</tr>
<tr>
<td>Conduct disorder</td>
<td>1.2</td>
<td>5.4</td>
<td>14.3</td>
</tr>
</tbody>
</table>

similar in the two groups, suggesting that the probands with depression only were no more likely to transmit alcoholism to their offspring than were the control probands. Probands with depression plus secondary alcoholism did not convey a greater risk of major depression or anxiety disorders to their offspring over the age of 18 than did probands with depression alone. However, offspring of the secondary alcoholics had a threefold greater risk of alcoholism than did offspring of probands with depression alone, and a fivefold greater risk of antisocial personality.

Application of proportional hazard analyses, which age-corrected the outcome data while simultaneously controlling for the sex of the offspring, interview status and year of birth, yielded similar results. Probands with secondary alcoholism were nearly three times more likely to transmit alcoholism to their adult offspring than were probands with depression alone (Cox, 1972; Lee, 1980).

Similar results emerged for the offspring aged 6–17. Despite the differences in methodology for diagnosis in this group, the results are highly similar to those for adult offspring. Younger children of probands with depression alone had higher rates of major depression, anxiety disorders and conduct disorder than did children of control probands. Rates of alcoholism were similar in the two groups. Younger children of probands with secondary alcoholism, on the other hand, had higher rates of alcoholism and conduct disorder than did children of probands with depression alone. Rates of major depression were not further increased in the children of secondary alcoholics. There was also a linear increase in rates of anxiety disorders among children across the proband groups. Rates of conduct disorder were increased among children of probands with depression alone and were further increased among children of secondary alcoholics.

There were no sex differences in the rates of diagnoses among the children under age 18. In the adult offspring, the rates of major depression and anxiety disorders were greater among women whereas the rates of alcoholism and antisocial personality were higher among men. As stated above, the effect of the sex of the offspring was controlled for in the statistical analysis of the effect of alcoholism in the proband.

Because of the similarity in the findings for the offspring aged 6–17 and those over age 18, the two groups were combined for the analysis of the significance of the above findings (Table 3). These results suggest that the increased risk of major depression and anxiety disorders in the offspring of the depressed probands can be attributed to the presence of depression and its concomitants in the proband. The presence of secondary alcoholism in the proband did not significantly increase the risk of either major depression or anxiety disorders in offspring. The presence of secondary alcoholism in the proband did, however, substantially increase the risk of alcoholism in the offspring. The rates of alcoholism in the offspring of probands with depression alone and in the offspring of controls were not different. Risks of antisocial personality-conduct disorder were significantly increased among offspring of probands with depression alone and were further increased among offspring of secondary alcoholics.

Thus, probands with depression alone transmitted depression but not alcoholism to their offspring whereas probands with depression plus alcoholism transmitted both depression and alcoholism to their offspring. This suggests that depression and alcoholism are not manifestations of the same underlying disorder in these families.

TABLE 3. Percentage of diagnoses in both age groups of offspring by the presence of depression and alcoholism in the proband

<table>
<thead>
<tr>
<th>Offspring</th>
<th>Control</th>
<th>Depression alone</th>
<th>Depression and alcoholism</th>
</tr>
</thead>
<tbody>
<tr>
<td>N at risk</td>
<td>(190)</td>
<td>(241)</td>
<td>(37)</td>
</tr>
<tr>
<td>Major depression</td>
<td>3.8‡</td>
<td>16.4</td>
<td>15.6</td>
</tr>
<tr>
<td>Alcoholism</td>
<td>9.8</td>
<td>8.6†</td>
<td>32.1</td>
</tr>
<tr>
<td>Any anxiety</td>
<td>6.7†</td>
<td>18.7</td>
<td>23.3</td>
</tr>
<tr>
<td>Antisocial personality-conduct disorder</td>
<td>1.6*</td>
<td>6.2†</td>
<td>32.1</td>
</tr>
</tbody>
</table>

* Significance values relate to differences between the first two columns.
† Significance values relate to differences between the last two columns.
‡ P < .05.
* P < .01.
† P < .001.
The effects of the presence of alcoholism in both parents are shown in Table 4. There was a highly significant linear change in the rates of alcoholism and antisocial personality-conduct disorder according to the number of parents with alcoholism. There was a twofold greater risk of alcoholism and a threefold greater risk of antisocial personality-conduct disorder among offspring when both parents were affected than when only one parent was affected. There was also an increase in risk of a similar magnitude for both disorders when comparing offspring of one alcoholic parent with those of no alcoholic parents. Alcoholism in either one or both parents was not related to an elevated risk of major depression among offspring. Similarly, in analyses not shown here, it was found that the presence of major depression in one or both parents was not related to an elevated risk of alcoholism among offspring.

Thus, these results strongly suggest that there is specificity in the effects of assortative mating among parents on disorders in their offspring. The increased risk of alcoholism and behavioral disorders cannot be attributed to the nonspecific detrimental effects of an environment in which two parents have psychiatric illnesses, because the offspring tend to develop the same disorders as their parents. This specificity could be related to modeling of parental behavior, genetic factors or both.

**Discussion**

The results can be summarized thus: (1) Rates of alcoholism and conduct disorder were increased among offspring under 18 of probands with alcoholism and depression. (2) Rates of alcoholism and antisocial personality were increased among offspring age 18+ of probands with alcoholism and depression. (3) Rates of major depression and anxiety disorders were not significantly higher among offspring of secondary alcoholics than among offspring of probands with depression alone. (4) Offspring of parents who were both alcoholics had a twofold greater rate of alcoholism and a threefold greater rate of antisocial personality-conduct disorder than did offspring with only one alcoholic parent, and a sixfold greater rate of alcoholism than did offspring with no alcoholic parents.

These findings show that, despite the different methodologies for diagnosing psychiatric disorders in the older and younger offspring, the results were remarkably similar for the two groups. Our results confirm previous studies of the familial aggregation of both depression and alcoholism. Compared with controls, there was a fourfold increased risk of major depression among offspring of primary depressives and a threefold increased risk of alcoholism among offspring of secondary alcoholics. The magnitude of increase in risk among offspring of the latter group is nearly as high as that observed for relatives of primary alcoholics (Goodwin, 1983).

As we have previously shown for the adult first-degree relatives (Merikangas et al., in press), depression and alcoholism do not appear to be alternate forms of expression of the same underlying illness. This was suggested by the finding that rates of alcoholism among offspring of probands with major depression alone were not greater than those observed among offspring of controls. The combination of the two disorders in the families of depressed probands with alcoholism, however, may not be independently transmitted. Some evidence suggested that specificity of transmission existed for the combination and the order of presentation of the two disorders among the adult first-degree relatives. We are currently analyzing whether such a combination occurs more commonly than would be expected by chance alone. If so, this combination may constitute a distinct subtype of affective disorder or alcoholism.

The high prevalence of alcoholism among offspring of the secondary alcoholics in this sample was notable. One-third of offspring aged 18+ received a diagnosis of alcoholism and the children under 18 were already beginning to manifest deviant drinking behavior. The results are particularly alarming considering the fact that these are clearly underestimates of the rates of alcoholism because 40% of the sample had not yet reached the age of 18 and thus had not passed through, if even entered, the period of risk for development of alcoholism.

The increased risk of alcoholism and conduct disorder in children of parents who both have alcoholism has not been previously reported. Similar effects of assortative mating on increased risk to offspring have been observed for affective disorders and schizophrenia (Fischer and Gottesman, 1980; Merikangas and Spiker, 1982; Weissman et al., 1984b).

Concordance between spouses for a disorder does not necessarily imply that assortative mating for that trait or for a correlate of that trait has occurred. Such

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**Table 4. Percentage of diagnoses in both age groups of offspring by the presence of alcoholism in parents**

<table>
<thead>
<tr>
<th>Disorders of offspring</th>
<th>N at risk</th>
<th>Major depression</th>
<th>Alcoholism†</th>
<th>Antisocial personality-conduct disorder†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Both alcoholics</td>
<td>(22)</td>
<td>13.6</td>
<td>36.4</td>
<td>31.8</td>
</tr>
<tr>
<td>One alcoholic</td>
<td>(91)</td>
<td>11.0</td>
<td>15.4</td>
<td>9.9</td>
</tr>
<tr>
<td>Neither alcoholic</td>
<td>(355)</td>
<td>9.3</td>
<td>6.5</td>
<td>2.8</td>
</tr>
</tbody>
</table>

† Test for linear trend: \(P < .001\).
PSYCHIATRIC DISORDERS IN OFFSPRING

Concordance could result from convergence for the trait as a result of marital interaction. If, however, one can demonstrate that the trait clusters in the first-degree relatives of the spouse with the trait who do not share the environment with the proband, then observed concordance can be attributed to assortative mating. From our data (Merikangas et al., in press), it was concluded that assortative mating had occurred because greater rates of psychopathology were observed among the relatives of the ill spouses than among those of the healthy spouses.

Regardless of the mechanism or specific traits involved in the observed concordance for alcoholism in these couples, our data suggest that such concordance is a potent risk factor for the development of alcoholism and antisocial personality-conduct disorder in offspring. Whether the increased manifestation of disorders results from increased genetic loading or detrimental environmental factors or both cannot be determined from our family study data. Nevertheless, the role of the presence of alcoholism in both parents should be considered in research and treatment involving their offspring.

The increased rates of conduct disorder in the younger offspring and of antisocial personality in the adult offspring of alcoholic probands confirm the association between these disorders reported from retrospective analyses of alcoholic probands (Alterman et al., 1982; Cadoret and Gath, 1978; Goodwin et al., 1975; Schuckit et al., 1972). The finding that children of parents with major depression have an increased risk of conduct disorder has also been previously reported (Connors et al., 1979; Puig-Antich et al., in press).

The finding in our study that most of the children (70%) with conduct disorder received other psychiatric diagnoses as well raises the question of whether conduct disorder is a nonspecific manifestation of psychopathology that is a reaction to the environmental instability resulting from psychiatric illness in one or both parents. Furthermore, if conduct disorders were a reaction to parental illness and its environmental concomitants, the risk of conduct disorder in children of one parent with two disorders or of two parents with psychiatric illness would be further increased, as was observed in our data.

Puig-Antich et al. (in press), on the other hand, argue that conduct disorder may be an early manifestation of affective disorder or alcoholism. The findings from the present study tend to support this. If conduct disorder were an expression of nonspecific behavioral pathology, most of the affected children would not develop antisocial personality in adulthood. Contrary to this expectation, however, our data appear to show that conduct disorder persists into the adulthood form of antisocial personality—the rates of childhood conduct disorder and adult antisocial personality were similar for offspring of depressives aged 6–17 and 18+, respectively, and doubled in offspring of secondary alcoholics.

The specificities of transmission of antisocial personality-conduct disorder and alcoholism observed in our data are suggestive of common underlying pathology for these disorders, as observed by Adler and Raphael (1983). However, the small number of children with conduct disorder in our study, the lack of direct interviews with the younger offspring and the large degree of overlap in the diagnostic criteria for these disorders preclude a definitive conclusion. Moreover, previous studies (Cloninger and Reich, 1983; Cloninger et al., 1979; Lewis et al., 1983) suggest the independence of alcoholism and antisocial personality. It is probable that conduct disorder is a heterogeneous category, being prodromal to affective disorders or alcoholism or both. It will be interesting to examine which of these children with conduct disorder later develop depression, alcoholism and antisocial personality.

We are currently conducting a longitudinal study using direct interviews with these children. Such data will enable us to address some of the questions raised above and to study the validity of the findings reported herein.

References

AMERICAN PSYCHIATRIC ASSOCIATION TASK FORCE ON NOMENCLATURE AND STATISTICS. Diagnostic and Statistical Manual of Mental Disorders (DSM-III), Washington, D.C., 1980.


