Chapter 4

Psychopathology in Offspring of Parents With Affective Disorders

Familial aggregation has been frequently observed among probands with depression, anxiety disorders, and alcoholism (Gershon et al. 1976; Goodwin 1983; Crowe et al. 1983). Because of the familial nature of these disorders, offspring of such probands have been identified to be at high risk for developing these illnesses themselves (Tarter 1983). Information regarding this risk has come from several sources: retrospective studies of patients with psychiatric disorders, studies of children whose parents are being treated for these disorders, and longitudinal follow-up studies of children with symptoms of the disorders.

Although most studies of high-risk children have been conducted with children of schizophrenic mothers, there is increasing evidence that children of parents with depression, alcoholism, and anxiety disorders are also at increased risk for psychopathology. Reviews of the literature have shown high rates of symptomatology and impairment in offspring of probands with major depression (Orvaschel et al. 1980; McKnew et al. 1979; Beardslee et al. 1983), with a prevalence of diagnosable illness in the offspring ranging from 33 to 45%, most of it affective in nature. A family history of depression appears to be the major risk factor for depression in children. Negative environmental factors such as family discord, instability, and disruption are consistently reported in retrospective studies of depressed adults and in studies of children with depression (Orvaschel et al. 1980).

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Children of alcoholic parents have an even greater risk of suffering from the numerous disorders than has been reported for children with depressed parents. Infants born to mothers who drink heavily during pregnancy may develop fetal alcohol syndrome, which is characterized by physical, emotional, and intellectual deficits (Steinhausen et al. 1982). Children of alcoholic parents have an approximately fourfold greater risk of developing alcoholism than children of nonalcoholic parents, with males at a much greater risk than females; the effects of paternal versus maternal alcoholism may differ as well (Cloninger et al. 1979). The unstable home environment in which these children are raised has likewise been well documented as characterized by family disruption, frequent divorce, and low socioeconomic status (Adler and Raphael 1983). An association between childhood conduct disorder and adult alcoholism has been demonstrated in retrospective studies of alcoholic persons and prospective studies of children with hyperactivity and conduct problems (Goodwin et al. 1975; Cadoret and Gath 1978; Alterman et al. 1982).

Although the risk of psychopathology in offspring of parents with anxiety disorders has not been established, studies of the relatives of adults with panic disorder, phobia, obsessive-compulsive disorder, and generalized anxiety disorder show an increased risk of anxiety disorder compared with normal populations (Crowe et al. 1983). However, the lack of specificity of transmission is notable for most of the disorders, with the exception of panic disorder and possibly obsessive-compulsive disorder. The diagnostic overlap both within the anxiety disorders and between anxiety disorders and affective disorders presents a major difficulty in interpreting family studies in this area. Weissman et al. (1984) found that children under the age of 18 of parents with depression and either agoraphobia or panic disorder had an increased risk of separation anxiety, panic disorder, and phobic disorders compared with children of parents with major depression only or normal controls. This finding has been confirmed in a more recent direct interview study of these children (Weissman et al. 1987a, 1987b).

Several studies have reported a link between childhood school refusal or separation anxiety and either phobic anxiety or panic disorder in adulthood (Berg et al. 1974; Gittelman-Klein 1975). In general, studies of the early history of agoraphobic adults report the onset of phobias before age 10 in a large proportion (Sheehan et al. 1981).

Although there is a consensus in the above studies that offspring of probands with the above-cited psychiatric disorders are at increased risk for psychopathology, there are few data regarding the mechanism

for the elevated risk. Twin and cross-fostering studies have established the involvement of genetic factors in at least some subtypes of these disorders. Also, the negative home environments of these children are noted throughout, and all of the major psychiatric disorders are related to major and chronic disruption in the parental role. Bothwell and Weissman (1977) reported that social role impairment of depressed women persisted up to 4 years after cessation of the acute episode of depression. Impaired marital functioning of both depressed and alcoholic patients has been a consistent finding. Thus, it is likely that genetic predisposition is potentiated by the detrimental environment that is so often characteristic of parents with these disorders.

One phenomenon related to both familial disruption and elevated risk to offspring is concordance for psychiatric disorders in parents. The present study therefore focused on the effects of parental concordance for psychiatric illness in general and affective illness in particular.

Previous reports from our family study of 215 probands and their 456 offspring over the age of 6 have shown that when parents are concordant for alcoholism, children are more likely to become alcoholic themselves and are also more likely to develop conduct disorder in childhood and antisocial personality in adulthood (Merikangas et al. 1985). Similar findings emerged for depression and anxiety disorders. There was a linear relationship between the number of ill parents and rates of depression and/or anxiety disorders in children (Weissman et al. 1984). However, these data were considered preliminary because the children had not been interviewed directly.

METHODS

Probands

The analysis reported herein is based on 133 white probands with major depression defined according to modified Research Diagnostic Criteria (RDC), who were in treatment at the Yale University Depression Research Unit or other facilities in the Department of Psychiatry. They were group matched by sex and age with 82 normal controls who had no history of psychiatric illness and who were obtained from the 1975 community survey by Weissman and Myers (1978). Complete pedigrees for each proband were systematically obtained, and diagnostic assessments according to RDC were made for every (living or dead) adult first-degree relative and spouse.

The depressed probands were classified according to the presence

or absence of other diagnoses, such as alcoholism and anxiety disorders. The onset of alcoholism in all of the probands was chronologically secondary to major depression. All probands with primary alcoholism or antisocial personality were excluded from the study. Anxiety disorder included agoraphobia, panic disorder, or generalized anxiety disorder and could have occurred either concomitant with or temporally separate from depressive episodes.

Direct interviews were obtained from adult relatives and spouses whenever possible. If not, family history data were obtained from multiple informants and from medical records. Direct interviews were conducted with 40% of the sample, and family history information was available from multiple informants in over 55% of the relatives. Diagnostic assessments of the relatives were made blindly with respect to status of the proband, using a best-estimate procedure (Leckman et al. 1982). Diagnoses of adult relatives and spouses were made according to modified RDC and were based on all available information.

At the time of the original study, offspring under age 18 were not directly interviewed, because diagnostic instruments and procedures for the assessment of psychiatric disorders in children were not available. A direct interview study of children was initiated 6 years after the original study had begun. All probands with offspring under age 18 at the time of the original proband interview were recruited for participation in the high-risk study. Eighty-seven percent of the eligible probands agreed to participate.

To determine the current clinical status and social functioning of the parents, each parent was interviewed separately by independent interviewers. A third interviewer interviewed a parent (preferably the mother) about the child and, at another time, interviewed the child about himself or herself, in order to obtain a comprehensive assessment of the child's psychiatric, behavioral, and social functioning. Parents were asked to complete self-administered reports about themselves and about each of their children, and children (approximately 10 years and over) were asked to complete self-administered reports about themselves. Authorized by both parent and child, we asked each child's teacher, pediatrician, and, when indicated, other health-care providers to complete questionnaires about the child. Direct interviews were obtained with 83% of the eligible children, and 97% of the children had a report from at least one parent. Eighty-four percent of the mothers and 72% of the fathers also completed the diagnostic interviews about themselves.

The interviewers had a minimum of 5 years of clinical experience with children and included two child psychologists, two child psychiatry fellows, and two masters-level school psychologists. They

were blind to the diagnostic status of the parent for the child interviews and blind to the clinical status of both the child and the previous data on parents for the interviews on current parent status.

Assessment of Children

Adapted for use in longitudinal studies as a reliable and valid instrument for obtaining lifetime diagnoses, the Kiddie-SADS-E (Puig-Antich 1982; Orvaschel et al. 1982; Chambers et al. 1985) and the DSM-III addenda were used in our pilot study at the Yale Psychiatric Institute to assess diagnoses in the children. Findings suggest that interviewing a parent and child separately and combining the results of the two interviews provide a more complete and accurate diagnostic assessment of the child. The Kiddie-SADS-E is the core of a comprehensive interview that we assembled to be administered to a parent about the child and to the child about himself or herself. A more detailed description of the assessment procedures of the children is given by Weissman et al. (1987a, 1987b).

Best-Estimate Diagnoses

A best-estimate diagnostic procedure was used in which a child psychiatrist and clinical psychologist who were not involved in the interviewing reviewed all sources of information and independently assigned a diagnosis. Discrepancies were resolved by a third source, who also independently and blindly reviewed all available information. We plan to reinterview all offspring and parents in 2 years. The initial level of agreement was 83%.

RESULTS

There were 215 probands in the original study, of whom 165 had offspring. Of these, 239 adult offspring were assessed in the original study with the SADS-L and Family History RDC, and 220 offspring ages 6–23 were assessed in the high-risk component of the study with the Kiddie-SADS-E, for a total of 459 offspring for whom diagnostic assessments were completed.

The age and sex distributions of the offspring are shown in Table 1. There were approximately equal numbers of male and female offspring, and most of the offspring were between the ages of 18 and 24. A substantial proportion of the offspring were well into adulthood. The number of children per family did not differ between the two proband groups.

The lifetime prevalence rates of disorders among the offspring according to the original proband group of their parent are shown in Table 2. There was a twofold increase in the rates of major depres-

sion among the offspring of depressed probands compared with normal probands. Major depression in the offspring was defined according to modified RDC as in our adult sample: four major symptoms; 4 weeks duration; and impairment. Anxiety disorders were also significantly more prevalent among offspring of the depressed probands. Rates of alcoholism and conduct disorder or antisocial personality were not significantly higher among the offspring of the depressed compared with the normal probands.

Because a large proportion of the spouses of both the depressed and normal probands also had psychiatric diagnoses and because of the large number of secondary diagnoses in the probands, disorders in the offspring were also examined according to the diagnoses of both parents, rather than by the original case-control design. Thus, normal control probands with spouses with psychiatric illness were reclassified by the diagnosis of their spouses. Table 3 shows the number of parents ill by diagnosis; these diagnostic groupings are

Table 1. Number of offspring by age and sex

	Age	Male	Female	Total
High-risk study	<12	20	15	35
	12–17	39	53	92
	18–24	46	47	93
Family study	18–24	58	52	110
	≥25	65	64	129
Total		228	231	459

Table 2. Proportion of offspring with diagnoses by proband group

	Diagnosis in proband parent	
Diagnosis in offspring	Depressed (n = 273)	Normal (n = 186)
Major depression	23.4*	11.3
Alcoholism	7.7	8.6
Conduct disorder/antisocial personality	15.8	10.7
Anxiety disorder	34.8*	22.6
Any psychiatric diagnosis	67.8*	52.2

Note. Values are percentages.
*$P < .01$.

not mutually exclusive. That is, in all of the couples in which both members were affected, at least one parent had major depression. From Table 3, it can be seen that concordance for major depression, anxiety disorders, and any psychiatric diagnosis was fairly common, whereas concordance for alcoholism was not. This may be attributed to the sampling of probands with major depression, in which primary alcoholism was an exclusion criterion.

Table 4 presents the rates of major depression and any RDC diagnosis among the first-degree relatives of the spouses of the depressed probands. This analysis shows that the relatives of the spouses with major depression had significantly higher rates of major depression and any RDC diagnosis than the relatives of the spouses who did not have major depression. Similarly, the relatives of the spouses with any RDC diagnosis also had a significantly increased risk of

Table 3. Parental mating types by diagnosis

Diagnosis in parent	Parental mating type (%)		
	Both	One	Neither
Major depression	15.7	50.9	33.3
Alcoholism	4.8	14.5	80.6
Anxiety disorder	10.3	44.2	45.5
Any psychiatric diagnosis	41.2	38.2	20.6

Note. n = 165 couples.

Table 4. Lifetime prevalence of psychiatric disorders among parents and siblings of spouses of probands with major depression

Diagnosis in spouse	Lifetime prevalence among first-degree relatives of spouse (%)	
	Major depression	Any RDC diagnosis
Major depression		
Present	4.8	25.5
Absent	1.4*	16.7*
Any RDC diagnosis		
Present	3.0	23.4**
Absent	1.3	12.5

Note. RDC = Research Diagnostic Criteria.
*$P < .05$, **$P < .001$.

any RDC diagnosis compared with the relatives of the spouses who did not meet RDC for any lifetime diagnosis. This suggests that there was familial aggregation of major depression and psychiatric illness in general in the families of the spouses who had major depression and those with any RDC diagnosis. From these results, one can conclude that it is likely that the concordance for major depression between the probands and their spouses can be attributed to assortative mating for depression or some related trait rather than to marital interaction resulting in the occurrence of depression in the spouse of the depressed proband.

Table 5 shows the relationship between any psychiatric illness in parents and disorders in offspring. The strongest linear trend was observed for any psychiatric diagnosis in offspring. That is, when neither parent was affected, one-third of the children had a diagnosis; when one parent was ill, over one-half of the children had a diagnosis; and when both parents were affected, three-quarters of their offspring had a diagnosable psychiatric illness.

Major depression, anxiety disorders, and antisocial personality/conduct disorder also showed significant linear trends according to the number of parents with any RDC diagnosis. Alcoholism was the only diagnostic category among children that was not related to parental concordance for any psychiatric diagnosis.

Table 6 shows the effects of parental concordance for alcoholism. There is a strong linear trend in the relationship of rates of alcohol dependence among offspring and the number of parents with al-

Table 5. Proportion of offspring with diagnoses by parental mating type for any psychiatric disorder

	Parental mating type for any psychiatric disorder			
Diagnosis in offspring	Both (n = 201)	One (n = 173)	Neither (n = 85)	χ^{2a}
Major depression	29.4	23.7	14.1	7.38*
Alcoholism	8.0	8.1	8.2	0.01
Conduct disorder/antisocial personality	17.4	14.5	3.5	8.51*
Anxiety disorder	41.8	23.7	14.1	25.99**
Any psychiatric diagnosis	75.1	57.8	36.5	39.05**

Note. Values are percentages.
[a]Linear trend in proportions, 1 df.
*$P < .01$. **$P < .001$.

coholism. Offspring with one alcoholic parent had a twofold increase in rates of alcoholism compared with offspring of parents without alcoholism. Likewise, offspring of couples concordant for alcoholism had a threefold increase in rates of alcoholism compared with those in which one parent was affected. Similarly for antisocial personality and conduct disorder, there was a strong significant linear trend according to the number of parents with alcoholism. Rates of major depression and anxiety disorders were not significantly increased among offspring of alcoholic parents.

The effects of parental concordance for alcoholism and any RDC diagnosis on the lifetime prevalence rates of diagnoses in offspring are summarized in Table 7. Alcoholism is the disorder for which parental assortative mating was associated with the greatest increase in the rate of the same disorder among offspring. Offspring with two alcoholic parents had a threefold increase in rates of alcoholism compared with offspring of couples in which only one parent had alcoholism. Nearly 50% of the offspring over age 18 of the couples concordant for alcoholism had alcoholism themselves, compared to 11% when neither parent had alcoholism. The effect of assortative mating for alcoholism was also seen in the increased risk of antisocial personality in the offspring over age 18: 30% had antisocial personality compared to 2% of the offspring of couples without alcoholism. There was a 1.7-fold increase in the risk of conduct disorder in the younger offspring and of antisocial personality in the older offspring of parents who were concordant for alcoholism.

Table 6. Proportion of offspring with diagnoses by parental mating type for alcoholism

Diagnosis in offspring	Parental mating type for alcoholism			
	Both (n = 25)	One (n = 84)	Neither (n = 350)	χ^{2a}
Major depression	28.0	17.9	18.0	.80
Alcoholism	32.0	10.7	5.7	18.77**
Conduct disorder/antisocial personality	36.0	21.4	10.3	18.07**
Anxiety disorder	44.0	32.1	28.3	2.67
Any psychiatric diagnosis	80.0	69.1	58.3	7.16*

Note. Values are percentages.
[a]Linear trend in proportions, 1 df.
*$P < .05$. **$P < .01$.

Table 7. Summary of effects of parental concordance for alcoholism on diagnoses in offspring

Concordance in parents	Diagnosis with increased prevalence in offspring	Relative risk (both vs. one parent with diagnosis)
Alcoholism	Alcoholism	3.0
	Conduct disorder (offspring ≤ age 18) or Antisocial personality (offspring > age 18)	1.7
Any diagnosis	Anxiety disorders	1.8
	Any diagnosis	1.3

Note. $N = 456$.

Last, parental concordance for any RDC diagnosis was related to extremely high rates of diagnoses in offspring, with an average of 70–80% being affected. Concordance for any RDC diagnosis in parents was related to a 1.8-fold increase in the rates of anxiety disorders and a 1.3-fold increase in the rates of any diagnosis in offspring compared with those in offspring with one parent ill.

DISCUSSION

The results indicate that parental concordance for psychiatric illness in general and alcoholism in particular is related to an increased risk of psychiatric disorders in the offspring. The findings from our earlier studies in which the information on children was derived from family history, rather than direct interviews, were confirmed in these analyses. The effects of parental concordance for major depression and anxiety disorders have been presented elsewhere (Merikangas et al. 1988).

Also consistent with earlier studies was a high degree of concordance for psychiatric illness among the parents, with 41% of the couples consisting of dual matings for psychiatric disorders (Merikangas 1982). Concordance between spouses for a disorder does not necessarily imply that assortative mating for that trait occurred. Such concordance could result from convergence for the trait as a result of marital interaction. However, evidence regarding aggregation of the trait among first-degree relatives of the spouse with the trait, who do not share the environment with the proband, would exclude the latter explanation. From our data, it was concluded that assor-

tative mating had occurred because increased rates of psychopathology were observed among the relatives of the ill spouses compared with those of the well spouses.

Concordance for a trait does not imply that mating has occurred for that particular trait. Rather, mate selection may involve another factor that may be a correlate or precursor to the trait for which concordance is assessed. Indeed, differential mate selection among persons with affective disorders is unlikely because the onset of these disorders in both spouses generally occurs several years after the time of marriage. We have previously suggested that mate selection in these couples may be related to personality factors that are premorbid to affective disorders or to similar levels of social differentiation (Merikangas and Spiker 1982).

These data clearly demonstrate that offspring of concordant parents are at significantly increased risk of developing psychopathology. We have also demonstrated some degree of specificity of transmission of the effects of assortative mating as well, with children exhibiting a tendency to develop the same disorders as those that are manifest in their parents. Such specificity may be attributable to shared liability, modeling of parental behavior, or a combination thereof.

Evidence for continuity between childhood and adulthood manifestation of similar syndromes was provided by the remarkably similar increase in the relative risks of disorders among the younger and older offspring of couples in particular mating classes. For example, similar elevations of risk were observed for conduct disorder among younger offspring and antisocial personality among adult offspring of dual-mated alcoholic couples compared with those of other parental mating types. In contrast, little continuity was observed between conduct disorder and antisocial personality among the younger and older offspring of parental mating for depression alone.

Although assortative mating among parents has been shown to be an important risk factor for the development of psychopathology in their children, the mechanism by which this increased risk occurs is not known. It is likely that assortative mating is related to both increased genetic risk and a clustering of environmental risk factors. Couples with concordance for affective disorders have been found to have significantly greater impairment in marital and social adjustment and an elevated divorce rate compared with couples in which only one member is affected (Merikangas et al. 1983; Merikangas 1984).

These data clearly demonstrate that offspring of parents concordant for psychiatric disorders are at significantly increased risk of developing psychopathology. The implications of these findings in terms

of primary prevention, the ultimate aim of high-risk studies, are not clear. Genetic counseling of prospective couples in which both have a family history of depression, anxiety disorders, or alcoholism is an unlikely intervention. However, efforts toward secondary intervention depend on the identification of the specific factors that comprise appropriate targets of prevention and intervention. Our study and those of others have identified the presence of parental concordance for depression, alcoholism, and other disorders as one such factor related to significantly increased risk in children. Efforts at identification of such situations by routine assessment of the spouse of patients who come for treatment and application of interventions that attempt to minimize the marital and parental role impairment may help to decrease the substantially elevated rates of psychiatric disorders in the children examined in this study.

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