The Course of Major Depression in the Offspring of Depressed Parents

Incidence, Recurrence, and Recovery

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• The 2-year course, first onset (incidence), recurrence, and recovery of major depression in 174 offspring at high and low risk for major depression were studied. A variety of predictors of course were examined, including parental diagnosis, demographic and clinical characteristics of the family and offspring, comorbidity and social functioning in offspring, and family risk factors. The 2-year incidence rate was 8.5%. All of the incident cases of major depression occurred in offspring of depressed parents. Additional predictors of incidence were a preceding diagnosis of conduct disorder and subclinical symptoms of depression. The recurrence rate results are tentative because of the small sample. The 2-year recurrence rate was 16.1%. Predictors of recurrence were a previous comorbid diagnosis of dysthymia or problems in social functioning. By the end of 2 years, the majority of offspring (87%) had recovered. The mean number of weeks to recovery was 54 in the offspring of depressed parents and 23 in the offspring of nondepressed parents. Offspring with an onset of major depression at age 13 years or younger, who were exposed to divorce in the family or who had been exposed to more than one parental depressive episode, had significantly more protracted times to recovery. We conclude that there are different predictors of incidence of major depression, its recurrence, and time to recovery in offspring, and that parental depression has an impact on the course in offspring.

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Longitudinal studies of depressed children and adolescents can provide important information for determining the nature and persistence of the illness and are useful for planning treatment and prevention. Ideally, these studies should use systematic diagnostic assessment and take into account the diagnoses of both parents. The latter is important because several recently published studies have clearly demonstrated that parental depression is a risk factor for depression in offspring.[1-5] These or other studies have also suggested that the age at onset, severity, recall of depression, and the impact of family risk factors, such as family cohesion or parent-child discord, may differ by parental diagnosis (V.W., M.M.W., P.W. and C. Caron, MD, unpublished data, 1982 to 1984).[6] In addition, the definition of clinical course in these studies should be precisely conceptualized and defined.[7,8] Clear distinctions between incidence, remission, and recovery are useful for comparisons of findings between studies. The rates and predictors between these outcomes undoubtedly differ.

Although there are no longitudinal studies that meet all these requirements, some data are available in samples of referred[9-19] or nonreferred[2,3,20-23] children. These studies show the persistence of depression, the consequences on overall functioning, and the impact of comorbidity with other psychiatric diagnoses on long-term outcome.

The study by Hammen et al[3] is the only published report of data on the effects of parental illness on the course of illness in the child. Ninety-two school-aged children of women with major depression, bipolar illness, or a chronic medical illness, and normal controls, were followed up for 3 years. Diagnostic interviews were conducted with the children every 6 months. The highest rates of depression were found in the offspring of depressed parents. The offspring had a pernicious course during the 3 years, rare prepubertal onsets, and an increasing frequency of depression beginning at age 12 years. The Hammen et al study is the first longitudinal study published with a high-risk design and multiple control groups, but, as with any study, there are limitations. The sample was small (only 22 children of depressed mothers); fathers were not assessed, and so nonrandom mating, which is likely to be high, could not be taken into account; and the assessment of children was not "blind" to the mother's diagnosis.

We report on the course of depression and its predictors in a nonreferred sample of offspring of depressed and nondepressed parents by examining the rates of first onset (incidence) of depression, the recurrence, and the time to recovery during a 2-year period. This report extends the findings of Hammen et al[3] in that we examined a range of possible predictors of the course of depression in offspring, took into account the diagnostic status of both parents, and conducted the assessments of the offspring without knowledge of the diagnostic assessment of the parent. The hypotheses tested are that (1) the predictors of the course of major depressive disorder (MDD) in offspring will vary according to whether or not the parent is depressed and (2) that different factors will predict different types of course, ie, incidence, recurrence, and recovery.

SUBJECTS AND METHODS

Sample

Offspring were selected for the study by virtue of the presence or absence of a lifetime history of major depression (based on Research Diagnostic Criteria) in their parents. A complete description of the probands (parents) and their assessment has been published elsewhere.[24] The depressed probands had received treatment at the Yale University Depression Research Unit (New Haven, Conn). The normal controls came from a 1975 community survey conducted in New Haven and had no history of psychiatric illness, based on at least four direct interviews (the last two

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using the Schedule for Affective Disorders and Schizophrenia–Lifetime criteria and Research Diagnostic Criteria) during an 8-year period. All probands were white and group matched by age and sex. Previous reports from this study compared 125 offspring of 56 depressed proband parents with 95 offspring of 35 nondepressed proband parents. In psychiatric assessments of probands and their spouses taken at the time of the study, when the offspring were assessed, three control probands and six spouses of control probands reported a lifetime history of major depression; the depressed parents from these nine families had 28 offspring. Thus, the sample consisted of 220 offspring from 91 families, who were between the ages of 6 and 23 years at initial interview (time 1), with 153 offspring from 65 families with one or more depressed parent and 67 offspring from 26 families with neither parent depressed.

Two years after the initial interview, all 91 families were contacted for a second interview (time 2). Eighty-five (93%) of the 91 families with a total of 203 offspring consented to participate at time 2. The present study on the course of major depression consisted of 174 offspring (79% of the total sample) about whom diagnostic information was obtained from direct interviews with offspring and/or parents at time 2. Detailed information about time 2 interviews has been provided elsewhere.[25] The 174 offspring included in the present study, and the 46 who did not participate, did not vary significantly by age, sex, or their parent proband diagnoses. However, the 46 offspring tended to come from families with a lower socioeconomic status than did the 174 offspring (73% vs 48%, χ^2=9.2, *df*=1, *P*=.002).

The age and sex distribution of the sample of 174 offspring included in these analyses did not vary by the parent proband diagnosis. More than two thirds of the sample were offspring of one or more depressed parent (n=121 [69.5%]), and one third (n=53 [30.5%]) were offspring of parents without a history of major depression. There were 95 girls (54.6%) and 79 boys (45.4%). Twenty-eight offspring (16.1%) were under 12 years of age, 76 (43.7%) were between 12 and 18 years of age, and 70 (40.2%) were between 19 and 23 years of age at initial interview. The offspring were approximately 2 years older at follow-up.

Diagnostic Assessment of Offspring

A version of the Schedule for Affective Disorders and Schizophrenia for School-Aged Children, Epidemiologic Version, modified to generate most *DSM-III* axis and diagnoses, formed the core of a comprehensive interview administered to the parent about the offspring and to the offspring about himself or herself. Interviewers were blind to the parent's diagnostic status. These analyses include five *DSM-III* diagnostic groups—major depression, any anxiety disorder (ie, separation anxiety, panic disorder, phobia, obsessive-compulsive disorder, and overanxious disorder), any conduct disorder, any substance abuse (ie, alcohol and drug abuse), and dysthymic disorder.

Diagnoses of offspring were based on the "best-estimate" procedure.[26] A clinical psychologist and a child psychiatrist, who were not involved in the interviewing and who were blind to the diagnostic status of the parent, reviewed all sources of information and independently assigned a lifetime *DSM-III* diagnosis for each offspring. Discrepancies were resolved by a third source, who also independently and blindly reviewed all available information. Interrater reliability between two psychiatrists for diagnoses was excellent for the major psychiatric disorders.[27]

Definition of Course of MDD in Offspring

Best-estimate diagnoses made at both time 1 and time 2 were used for these analyses. *First onset* (incidence) of MDD was defined as no evidence of MDD currently or in the past at time 1 and a first onset between time 1 and time 2. In deriving incidence rates, all cases of MDD identified at time 1, current or lifetime, were eliminated from the denominator. *Recurrence* of MDD was defined as an episode of MDD in the year of the time 1 interview with a subsequent period of *remission*, defined as an asymptomatic period of at least 8 weeks, and an additional episode in the 2-year follow-up period between time 1 and time 2. The 8-week period for remission was selected as the definition according to the *DSM-III* criteria. *Time to recovery* was defined as the duration of the index episode at the time 1 interview in weeks, including retrospectively observed portions of that episode, until there was a remission as defined above.

Predictors of Onset and Course at Time 1

Parental depression, as previously defined, was examined as a predictor.

The maximum number of the mother's and father's episodes of major depression was used as a predictor. The score was trichotomized into 0, 1, or 2 or more episodes, because of the small number of parents experiencing more than two episodes. For most of the analyses, only the comparison of the effect of being exposed to two or more episodes, as compared with one episode, was explored.

Age of offspring was studied as a predictor; for some analyses, age was divided at 16 years, and in others, it was treated as a continuous measure.

A five-point scale based on the Hollingshead two-factor index of social position was used to measure socioeconomic status of the family.[28] Families in upper and middle social classes (social classes I, II, and III) were compared with families of lower social class (ie, IV and V).

For the analyses examining comorbidity in offspring as a predictor of recurrence and recovery, the sample included offspring with major depression in the year of the time 1 interview who also had comorbid diagnoses during the same period.

Clinical features of the offspring's depression were also examined as a predictor. Age at onset of MDD in the offspring was divided at less than 14 years on the basis of previous findings of increased risk in the less than 14-year-old age group.[29] The duration of the longest episodes of MDD in the offspring was divided at less than 1 year and examined as a predictor of recurrence and recovery. The offspring's number of episodes of depression was trichotomized into 0, 1, and 2+, with the expectation that offspring with more episodes would be at higher risk for recurrence and have a shorter time to recovery. Finally, the type and number of major depressive symptoms based on the Schedule for Affective Disorders and Schizophrenia for School-Aged Children were examined as predictors.

Subclinical depression was used as a predictor for the incidence analysis only. Offspring with depressive symptoms meeting probable, but not definite, *DSM-III* criteria at time 1 because of insufficient number of symptoms or duration were considered to have subclinical symptoms of depression. Offspring with subclinical symptoms of depression were compared with those offspring with no symptoms of depression as a predictor of an incident case in the follow-up period.

The Children's Global Assessment Scale (C-GAS), with a range of 1 to 100 (with higher scores indicating better functioning), was designed to measure overall functioning in the offspring.[30] Bird et al,[31] on the basis of discriminant function analysis, recommended a cutoff of 61 if the C-GAS is used as a dichotomized score. The C-GAS scores used in this study are based on the child psychiatrist's best estimate of average lifetime functioning at time 1. Associations between impairment in overall functioning, as indicated by a C-GAS score less than 61 at time 1, and rates of incidence, recurrence, and time to recovery were examined.

The Social Adjustment Inventory for Children and Adolescents is a semistructured interview designed for school-aged children or for parents about their children.[32] Offspring's functioning in school, spare-time activities, with peers, with siblings, with the opposite sex, and with parents is assessed for a 1-year period. Scores ranged from 1 to 4 in each area, with highest scores indicating more impairment. For this study, either the parent's or offspring's report of a problem was considered a positive score. The global scores for each role area were dichotomized, and 2-year incidence and recurrence rates and time to recovery were compared by presence or absence of problems in offspring.

Family Risk Factors

Parents and offspring completed a battery of self-report measures at time 1 and time 2. These measures were used to construct family risk factors (see Fendrich et al[6] for details). Included were (1) an index of poor marital adjustment based on parent reports on the Short Marital Adjustment Test[33]; (2) divorce based on parent's reports of marital history; (3) parent-child discord based on mother's reports on a family life events questionnaire; (4) "affectionless control" based on the caring and overprotection subscales of the Parental Bonding Instrument[34]; and (5) "low cohesion" based on the cohesion subscale of the Family Adaptability and Cohesion Evaluation Scale.[35] The association between the presence of these risk factors at the initial interview and incidence, recurrence, and time to recovery was assessed.

Statistical Methods

Initially, χ^2 statistics were used to test associations between outcomes and predictor variables for categoric data (ie, rates of recurrence or incidence by the presence or absence of a predictor). In addition, predictors were looked at simultaneously in a maximum likelihood logistic regression, with the use of the SAS LOGIST procedure predicting incidence.[36] The antilogarithm of the regression coefficient for the predictor yields an odds ratio for evaluating the impact of the predictor.

The cumulative probability of recovery by time since onset of a depressive episode was estimated by the Kaplan-Meier method.[37] Equality of survival distributions for different groups was tested by means of the log-rank test for homogeneity, which weights greater survival times more heavily, and the Wilcoxon test, which places more weight on early survival times.

RESULTS

Two-Year Incidence of Major Depression

Demographic and Clinical Predictors.—The 2-year incidence rate for MDD in the offspring was 8.5% (Table 1). All 10 of the incident cases of MDD came from the families with one or more parent depressed. Within the high-risk group, the 2-year incidence of MDD was 13.2 per 100.

***DSM-III* Disorders at Time 1.**—Many of the offspring without MDD at time 1 had other *DSM-III* disorders. Fourteen (11.9%) of 118 had conduct disorder, 29 (24.6%) had an anxiety disorder, six (5.1%) had either alcohol or other drug abuse, and nine (7.6%) had dysthymia. Offspring with previous conduct disorder, anxiety disorder, or dysthymia were more likely to have first onsets of MDD in the 2-year period than were offspring without these disorders. Only the association with conduct disorder reached statistical significance. Approximately 28% of the offspring with conduct disorder at time 1 as compared with 5.8% of those without had first onsets of MDD. Offspring with depressive symptoms not meeting criteria for MDD at time 1 had considerably higher incidence rates of MDD (30.7%) as compared with offspring who were asymptomatic at time 1 (5.7%) ($P<.01$, Fisher's Exact Test).

Social Functioning.—There were no significant differences in incidence of MDD by degree of impairment in offspring at time 1 as measured by the C-GAS or the Social Adjustment Inventory for Children and Adolescents.

Family Risk Factors.—Incidence rates of MDD in offspring did not differ by their exposure to the five family risk factors, ie, poor marital adjustment, divorce, parent-child discord, affectionless control, and low family cohesion.

Multivariate Analyses.—In the multivariate and bivariate analyses, only conduct disorder at time 1 and subclinical depressive symptoms predicted incidence cases in the offspring during the follow-up period. The age- and sex-adjusted odds ratios for being an incident case if the offspring had a preexisting conduct disorder were 18.1 (95% confidence interval, 3.85 to 72.9), and for subclinical depressive symptoms they were 7.38 (95% confidence interval, 2.07 to 29.0).

Recurrence of Major Depression

The 2-year recurrence rate of major depression in offspring was 16.1% (Table 2). The small sample limits conclusions, and the following results must be seen as tentative.

Demographic and Clinical Predictors.—Rates of recurrence in offspring did not vary significantly by parental depression. Because there were only eight offspring from nondepressed families and only one recurrence occurred in that group, all subsequent analyses were subset to families with depressed parents. There was nearly a twofold difference (although not significant) in offspring exposed to parents with two or more episodes (21.4%) vs those exposed to one episode (11.1%).

Comorbidity in Offspring.—Three (9.7%) of the 31 offspring had comorbid anxiety disorder, two (6.4%) had comorbid substance abuse, and two (6.4%) had comorbid conduct disorder. Nine (29%) of the 31 offspring had comorbid dysthymia at time 1. Offspring with comorbid dysthymia at time 1, as compared with offspring without it, had significantly higher rates of recurrence (50.0% vs 5.9%; $P<.05$, Fisher's Exact Test). In all but one case, the onset of the dysthymia either preceded or was in the same year as the onset of the major depression.

Clinical Features of MDD at Time 1 in Offspring.—The median age at onset of major depression for the 31 offspring depressed at time 1 was 14.6 years, and the age range was 5 to 23 years. Not shown here, neither earlier onset (defined as an onset before 14 years of age) nor duration of MDD greater than 1 year was found to be associated with higher rates of recurrence of depression. There was a nonsignificant trend for offspring with two or more previous episodes to be more likely to have recurrences than were offspring with only one previous episode (23.5% vs 7.1%). Neither type nor number of depressive symptoms reported by offspring during a direct interview at time 1 predicted recurrence in the follow-up period.

Social Functioning.—Offspring with overall impairment as rated by the C-GAS score at time 1 had higher rates of recurrence than did offspring without impairment (25.0% vs 0.0%), although the difference was not significant. Other problems at time 1, as assessed more specifically by the Social Adjustment Inventory for Children and Adolescents, significantly increased the risk of recurrence of MDD, including problems with spare-time activities, problems with peers, problems with the opposite sex, and problems with parents.

Family Risk Factors.—Exposure to family risk factors at time 1 did not increase the risk of recurrence of MDD.

Time to Recovery of Major Depression

The average time to recovery in the sample of 31 offspring depressed at time 1 was 46 weeks, the median was 12 weeks, and the range was 2 to 312 weeks. In some cases the offspring's episode had its onset before time 1; hence, some recovery times are longer than the 2-year follow-up period. Approximately 61% recovered after 6 months, 74% after 1 year, and 87% after 2 years. Four offspring took longer than 2 years to recover.

Demographic and Clinical Predictors.—The mean time to recovery was 54 weeks in the depressed offspring of depressed parents and 23 weeks in the depressed offspring of nondepressed parents. The majority (23 of 31) of depressed offspring in this sample had parents who were also depressed. Depressed offspring of parents with two or more episodes of MDD as compared with one episode had significantly protracted times to recovery (generalized Wilcoxon=3.93, $P=.04$; log rank=5.17, $P=.02$) (Fig 1). The mean time to recovery was 78.5 weeks for offspring of parents with two or more episodes and 16.0 weeks for offspring of parents with only one episode. Recovery time from MDD in the offspring did not significantly differ by sex or age of offspring, duration, number of episodes, type of symptoms of MDD in offspring, or social class of the family. Offspring with an early age at onset, 13 years or younger, had significantly protracted times to recovery compared with offspring with onsets past the age of 13 years (generalized Wilcoxon=4.63, $P=.03$; log rank=4.39, $P=.04$) (Fig 2). The mean time to recovery was 74 weeks in offspring with an age at onset of

Table 1.—Two-Year Incidence Rates for Lifetime Major Depression by Demographic Characteristics, Diagnoses, Social Functioning, and Family Risk Factors at Time 1*

	Incidence/No. (%)
Overall rate	10/118 (8.5)
Parent proband	
≥1 MDD	10/76 (13.2)†
Neither MDD	0/42 (0.0)‡
No. of parental episodes	
1	4/55 (7.3)
≥2	6/44 (13.6)
Sex of child	
F	5/56 (8.9)
M	5/62 (8.1)
Age of child, y	
≤16	4/68 (5.9)
≥17	6/50 (12.0)
SES	
I, II, III	3/60 (5.0)
IV, V	7/58 (12.1)
Psychiatric disorder and overall impairment, time 1	
Subclinical symptoms	
No	6/105 (5.7)
Yes	4/13 (30.7)§
Conduct disorder	
No	6/104 (5.8)
Yes	4/14 (28.6)‖
Any anxiety disorder	
No	6/89 (6.7)
Yes	4/29 (13.8)
Any substance abuse	
No	10/112 (8.9)
Yes	0/6 (0.0)
Dysthymic disorder	
No	9/109 (8.3)
Yes	1/9 (11.1)
C-GAS	
≥61	9/101 (8.9)
<61	1/25 (5.8)
Problems in role areas, time 1	
School	
No	7/81 (8.6)
Yes	3/37 (8.1)
Spare-time activity	
No	9/90 (10.0)
Yes	1/28 (3.6)
With peers	
No	9/98 (9.2)
Yes	1/20 (5.0)
With opposite sex	
No	9/113 (8.0)
Yes	1/5 (20.0)
With siblings	
No	7/101 (6.9)
Yes	3/17 (17.6)
With parents	
No	10/99 (10.1)
Yes	0/19 (0.0)
Family risk factors, time 1	
Poor marital adjustment	
No	4/47 (8.5)
Yes	4/54 (7.4)
Divorce	
No	6/85 (7.1)
Yes	4/33 (12.1)
Parent-child discord	
No	9/89 (10.1)
Yes	1/28 (3.5)
Affectionless control	
No	4/71 (5.6)
Yes	3/27 (11.1)
Low family cohesion	
No	4/54 (7.4)
Yes	3/45 (6.7)

*MDD indicates major depressive disorder; SES, socioeconomic status; and C-GAS, Children's Global Assessment Scale.
†Crude relative risk not estimable.
‡$P<.05$, Fisher's Exact Test, two tailed.
§$P<.01$, Fisher's Exact Test, two tailed. Crude relative risk, 5.38.
‖$P<.05$, Fisher's Exact Test, two tailed. Crude relative risk, 4.93.

13 years or younger, as compared with 26 weeks for offspring with onsets past the age of 13 years. The mean time to recovery for offspring with MDD and dysthymia at time 1 was 14.1 weeks as compared with 59.1 weeks for offspring with MDD without dysthymia. The two curves, however, were not statistically different from one another. The prevalence rates for the other comorbid disorders were too low to include them in these analyses.

Social Impairment.—Time to recovery from MDD in offspring was not predicted by time 1 impairment as assessed by the C-GAS or the Social Adjustment Inventory for Children and Adolescents.

Family Risk Factors.—Of the five family risk factors examined, only exposure to a divorce in the family was significantly associated with longer time to recovery in offspring (generalized Wilcoxon=7.85, $P=.005$; log rank=4.07, $P=.04$). The mean time to recovery was 66.7 weeks for offspring exposed to divorce and 29.0 weeks for offspring not exposed to divorce.

COMMENT

Limitations

Our findings have to be considered within the study's limitations. While this is the largest offspring study of depressed parents, and also one of the few with a longitudinal design, a sample of 174 offspring with a broad age range is still quite small for making predictions. It is reasonable to expect that factors predicting incidence, recovery, and recurrence will vary according to the offspring's age. A larger sample would have allowed us to examine possible developmental differences more closely. In the subsample of 31 depressed offspring, in which we looked at recurrence and time to recovery, the majority of the offspring were from depressed families and were female. The power to detect differences by depression status of the parent or sex of the child in this subsample was limited. If we had a larger sample, it would have been appropriate to look at the risk of recurrence by means of a life-table approach, taking into account the length of time in remission. Finally, the family risk factors used as predictors are not exhaustive. Even with these limitations, comparisons of our findings with other related studies show an emerging picture of offspring at high risk for MDD, as will be discussed.

Implications and Comparisons with Other Studies

Incidence.—Our 2-year incidence rates of MDD are comparable with the 1-year incidence rates found in the young adult population (aged 18 to 23 years) of the New Haven site, where most of these offspring lived, of the Epidemiologic Catchment Area study (8.5% vs 8.1%, respectively). While a history of parental depression has been found to be an important risk factor for MDD in offspring in many studies, the previous studies have been cross-sectional and,

Table 2.—Two-Year Recurrence Rates in Offspring of Depressed Parents for Lifetime Major Depression by Demographic Characteristics, Diagnoses, Social Functioning, and Family Risk Factors at Time 1*

	Incidence/No. (%)
Overall rate	5/31 (16.1)
Parent proband	
≥1 MDD	4/23 (17.4)
Neither MMD	1/8 (12.5)
No. of parental episodes	
1	1/9 (11.1)
≥2	3/14 (21.4)
Sex of child	
F	3/16 (18.7)
M	1/7 (14.3)
Age of child, y	
≤16	2/9 (22.2)
≥17	2/14 (14.2)
SES	
I, II, III	0/10 (0.0)
IV, V	4/13 (30.7)
Psychiatric disorder and overall impairment, time 1	
Conduct disorder	
No	4/21 (19.0)
Yes	0/2 (0.0)
Any anxiety disorder	
No	4/22 (18.2)
Yes	0/1 (0.0)
Any substance abuse	
No	3/22 (13.6)
Yes	1/1 (100.0)
Dysthymic disorder	
No	1/17 (5.9)
Yes	3/6 (50.0)†
C-GAS	
≥61	0/7 (0.0)
<61	4/16 (25.0)
Problems in role areas, time 1	
School	
No	1/13 (7.7)
Yes	3/10 (30.0)
Spare-time activity	
No	0/14 (0.0)
Yes	4/9 (44.4)‡
With peers	
No	1/17 (5.9)
Yes	3/6 (50.0)†
With opposite sex	
No	2/21 (9.5)
Yes	2/2 (100.0)§
With siblings	
No	2/19 (10.5)
Yes	2/4 (50.0)
With parents	
No	0/18 (0.0)
Yes	4/5 (80.0)‖
Family risk factors, time 1	
Poor-marital adjustment	
No	2/7 (28.5)
Yes	1/8 (12.5)
Divorce	
No	2/10 (20.0)
Yes	2/13 (15.3)
Parent-child discord	
No	2/13 (15.3)
Yes	2/10 (20.0)
Affectionless control	
No	2/15 (13.3)
Yes	2/6 (33.3)
Low family cohesion	
No	1/7 (14.2)
Yes	3/14 (21.4)

*MDD indicates major depressive disorder; SES, socioeconomic status; and C-GAS, Children's Global Assessment Scale.
†$P<.05$, Fisher's Exact Test, two tailed. Crude relative risk, 8.47.
‡$P<.05$, Fisher's Exact Test, two tailed. Crude relative risk, not estimable.
§$P<.05$, Fisher's Exact Test, two tailed. Crude relative risk, 10.52.
‖$P<.01$, Fisher's Exact Test, two tailed. Crude relative risk, not estimable.

thus, subject to recall bias. The cross-sectional findings that parental depression is a risk factor for depression in offspring are strengthened by these longitudinal findings that all of the incident cases of depression in offspring occurred in the offspring of depressed parents.

The importance of subclinical depression as a predictor of first onset of MDD paralleled others' findings. For example, Murphy et al,[38] in a 16-year follow-up study of adults living in Stirling County (Canada) reported that subjects with prodromal symptoms at baseline were approximately three times more likely to be incident cases than were subjects who were asymptomatic at baseline. The Epidemiologic Catchment Area study found that depressive symptoms not meeting criteria for major depression were among the single most important predictors of first-onset MDD 1 year later. Subjects with depressive symptoms at time 1 were more than four times as likely to develop a first onset of MDD 1 year later.[39] Together, the findings from several studies suggest that mild depressive symptoms, regardless of the age when they occur, frequently are a precursor of major depression.

Impact of Double Depression on Recurrence.—The high co-occurrence of dysthymia and MDD, "double depression", has been found consistently in clinical and epidemiologic samples of adults,[40,41] and more recently in children, and has been shown to have a high morbidity. Like Kovacs et al,[10] in their study of children, we found that offspring with major depression that was comorbid with dysthymia were at increased risk for recurrence. These findings are similar to those from the National Institute of Mental Health Collaborative Study on the Psychobiology of Depression, despite the considerable age differences in the sample. Both Kovacs et al[10] and Keller et al[2] (the latter in a separate study of nonreferred adolescents) found, as we did, that in the majority of cases the onset of the dysthymia preceded the onset of the MDD. Our 2-year recurrence rate for MDD was 16.2%, which is comparable with the 23% reported by Hammen et al[3] in their 3-year follow-up.

Recovery.—Our 1- and 2-year recovery rates of 74% and 87% from MDD were comparable with those reported by Keller et al[2] in their nonreferred sample of adolescents (median age, 14 years), where the 1- and 2-year recovery rates were 79% and 90%, respectively. The 1-year recovery rate from MDD of 74% was comparable with the 76.4% reported by Sargent et al[42] from the Epidemiologic Catchment Area study, a probability sample of adults, including treated and nontreated persons. Lower 1-year recovery rates of 60% were found by Kovacs et al[9] in their study of more severely ill treated children, but by the second year 92% had recovered. Keller et al[43] also found lower recovery rates in their follow-up of more severely ill treated patients, where over 50% had recovered. Taken together in

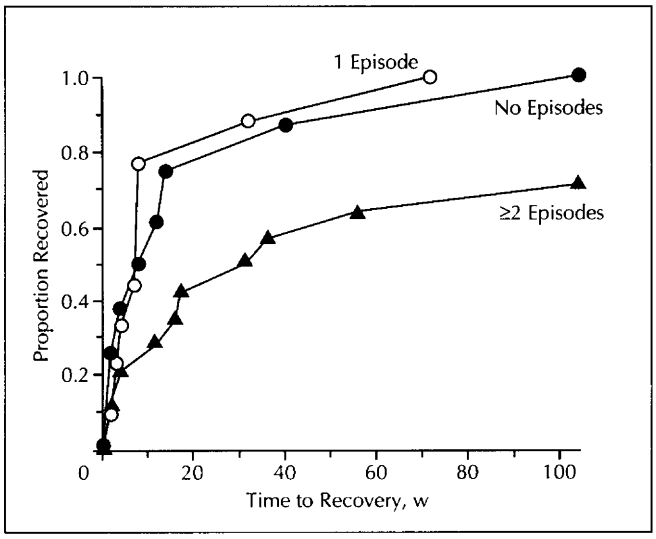

Fig 1.—*Recovery from major depression in offspring by number of parental episodes of major depression.*

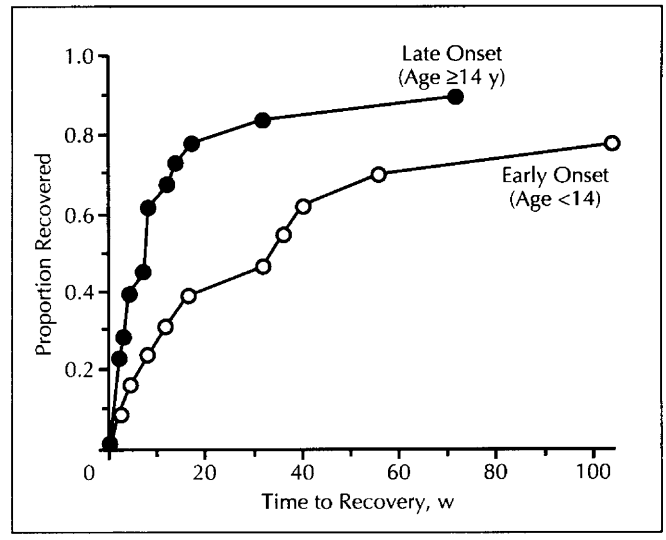

Fig 2.—*Recovery from major depression in offspring by age at onset in offspring.*

these five studies, a consistent picture is emerging that suggests that 1 year after onset of MDD, about 20% to 50% of children, adolescents, and adults with a major depression will not have recovered.[2,9,42,43] By 2 years, the figure will be reduced to 8% to 10%.

We also found differences in time to recovery from MDD in offspring by number of parental episodes of major depression. This is consistent with the findings of Keller et al on the impact of chronicity and severity of parental illness on children.[44] Although Keller et al did not look at time to recovery per se, they did find a deleterious impact of the number of parental episodes on children's illness and adaptive functioning.

In a retrospective assessment of course of MDD, Keller et al,[2] drawing on a variety of sources, including adolescent offspring of depressed patients, acquaintances of relatives of probands, community groups from the same neighborhood, and families enrolled in a health maintenance organization, found similar recovery rates in the adolescents, regardless of where sampled. Thus, they did not find a difference in time to recovery in adolescents of depressed parents. The difference in findings between studies may be due to the fact that they did not look at recovery stratified by number of parental episodes of MDD.

Like Kovacs et al,[10] we found that recovery did not differ by age and sex of offspring but that an early age at onset predicted longer time to recovery. As noted by Kovacs et al, this finding challenges the belief that younger children have only brief, transient depression. Like Kovacs et al and Keller et al, we found that double depression did not affect recovery. In fact, like Keller et al, we found a nonsignificant trend for shorter, and not longer, recovery time in the offspring with double depression.

Social Functioning.—Impairment in functioning was associated with increased risk of recurrence, but not with incidence or time to recovery. Numerous studies have suggested that impaired social functioning is associated with persistent depression in children.[16,21,45,46] All five offspring in our sample who had a recurrence of MDD during the 2-year period were rated as impaired on the C-GAS at time 1, and four of the five had double depression as well. The impairment rating and the increased risk of recurrence may be a consequence of comorbidity and not of major depression alone, since the severity of the MDD in offspring did not predict recurrence. Major depression with only mild impairment in functioning may be less likely to recur.

Family Risk Factors.—The absence of an effect of family risk factors on risk of incidence of MDD in offspring is likely to be an artifact of sample size and the fact that we had no incidence cases in the offspring in nondepressed parents. Previously, in our cross-sectional examination of these data, we showed that family risk factors were considerably more powerful predictors of MDD in the offspring of nondepressed than depressed parents[6] and that family risk factors in the offspring of depressed probands only had an impact when they occurred in combination (V.W., M.M.W., P.W, and C. Caron, MD, unpublished data, 1982 to 1984).

Of the family risk factors, only divorce was associated with an increased risk for a protracted time to recovery. Divorce in the family was associated with either parent having one or more episode of depression as compared with no depression in either parent (37.6% vs 7.1%; relative risk, 5; $P=.02$). Divorce, however, was not associated with the number of episodes of depression of the parent.

Clinical Features of the Depression.—For the most part, clinical features of the offspring's depression had little effect on recurrence or time to recovery from MDD. Only early age at onset of the offspring's depression was associated with an increased risk for a protracted time to recovery. There was significant overlap in the sample between those offspring with early onset of depression and those offspring exposed to two or more episodes of parental depression. Seventy-one percent of the offspring exposed to two or more episodes of parental depression had onset of MDD before the age of 14 years. Only 22% of the offspring exposed to one episode of MDD had an age at onset of MDD of less than 14 years ($P<.05$). This could partially explain the association of early-onset MDD in the parent and early-onset MDD in the child previously documented by this group.[5,29] The early onset of MDD in offspring and the recurrence of MDD in the parent, both of which delayed the recovery of the offspring, may be more powerful descriptors of illness severity than the actual clinical features of the offspring's depression. These findings would be consistent with family genetic studies that have shown higher familial loading of MDD by age at onset or by number of episodes of MDD in probands but have

not shown that particular symptom features of MDD increases risk in relatives.[47]

CONCLUSION

There is an emerging consensus that the course of early-onset depression is not benign and has a high recurrence rate.[2,3,10,17] Whereas there is now reasonably good information on the course of MDD in adult patients, comparable information in younger patients is scanty. Our findings highlight the need for more information in larger and younger samples. These studies must take into account the parental diagnosis and define precisely the different types of course. The latter will allow comparisons between studies as well as differentiation of predictors. The information that could be derived from large longitudinal studies of children at risk for depression or of depressed children, taking into account parental diagnosis, would be useful for planning rational treatment and prevention for young persons.

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