Onset of Major Depression in Early Adulthood
Increased Familial Loading and Specificity

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- In a family study of 133 probands with major depression and 82 normal control subjects, and 1,518 of their first-degree relatives, we found a substantial inverse relationship between the age of onset of major depression in the probands and the risk of major depression in their relatives. The relatives of probands whose onset of major depression occurred when they were younger than 20 years of age had the highest risk of major depression, compared with the relatives of probands who had later ages of onset or with the relatives of normal subjects. Probands with an age of onset of 40 years or more had familial loading that was only slightly higher than the families of normal control subjects. Our statistical methods enabled us to examine the relationship of the ages of onset in the probands and their relatives while accounting for possible confounding factors. More studies will be needed to sort out secular changes in the rates of the occurrence of major depression among young persons (cohort effect) from the high familial loading of major depression that has its onset in childhood and adolescence, and to determine whether the specificity of transmission of early-onset depression is the result of a single homogeneous disorder.

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There is converging evidence that some types of major depression can have their onset in childhood and adolescence, and that these early-onset forms may be associated with the high familial loading of major depression. Many of the earlier family studies did not examine the effects of depression in probands whose onset of depression was in childhood or adolescence, because of the commonly held view that depression was more apt to occur in middle age than in childhood.

Recent evidence for the presence of major depression in children and adolescents comes from the systematic study and follow-up of children who are treated, epidemiologic studies of children and adolescents, and data from the Epidemiologic Catchment Area (ECA) study that showed that the highest current rates of major depression in three US communities were found among subjects who were 18 to 44 years of age. The epidemiologic data also suggested that there has been an increase in major depression in the age cohort that came to maturity after World War II.

Evidence for a relationship between high familial loading for depression and an early age of onset has come from two different sources.

1. Studies in which adult probands were divided by the early and late onset of major depression and compared with a control group, and the rates of major depression in first-degree adult relatives and children were presented. With the exception of a recent study by Gershon et al., these studies have found that early-onset disorder in the proband increases the risk of major depression in the relatives, and, with few exceptions, the age of 40 years is the cutoff for early and late onset.

2. Studies in which the depressed probands were children or adolescents, and the rates of major depression in their adult relatives were examined. These recent studies have reported rates of major depression as high as 50 per 100 in the adult relatives of depressed adolescent probands. Although agreement is not unanimous, most studies have found that the early onset of depression in a proband, regardless of the cutoff age for early or late onset, increases the risk of major depression in the relatives.

Following the emergence of data on the presence of high rates of major depression in younger populations, in the present study we have examined the effects of the age of onset in probands who have major depression on the rates and onset of major depression in their first-degree relatives, including children 6 years of age and older. The primary focus is the association between the age of onset of depression in probands and the age of onset of major...
depression in their relatives.

The following features distinguish this study from most others:
1. The age of onset in probands has been examined by decade rather than by the dichotomization of the onset at 40 years of age.
2. The first-degree relatives include probands' children who were 6 years of age and older, as well as the adult relatives.
3. Possible confounding variables that could have biased the results, such as assortative mating and cohort effects, have been examined.
4. The interaction between the age of onset in relatives and the age of onset in probands has been examined using statistical techniques that combine survival analysis and log-linear models that have not been applied to previous studies of psychiatric disorders, to our knowledge.

The results show that there is a substantial inverse relationship between the age of onset of major depression in the probands and the rates of occurrence of major depression in relatives, with an onset that occurs before the age of 20 years having the highest familial loading and an onset at the age of 40 years and older having familial loading similar to that in the families of normal control subjects. Moreover, there is some specificity in the transmission, in that relatives of the probands with an earlier onset were more likely to have had the early onset of depression as well.

SUBJECTS AND METHODS

The full details of the design, assessment criteria, and procedures have been described elsewhere. Briefly, as part of a family study of major depression, blind diagnostic estimates were made for a total of 1,381 adult, first-degree relatives (parents, siblings, and children 18 years of age or older) and 194 children (6 to 17 years of age) of 215 probands (total, 1,518 first-degree relatives). There were 133 probands who had major depression; 89 of the 133 depressed probands had never been hospitalized, and 44 of the 133 depressed probands, on some occasion, had been hospitalized for major depression. All of the probands were white and were group matched to the control subjects for age and sex. Since no differences were found in rates of illness in relatives of the hospitalized and ambulatory depressed probands, the groups have been combined for this analysis. Eighty-two of the probands, who were drawn from a community sample, had no current or past psychiatric disorder other than normal control probands.

The design of the original case-control family study required that lifetime psychiatric diagnoses be made blindly of all adult first-degree relatives of each proband using direct interviews, a family history that was obtained from multiple informants, and medical records, when permission was granted. A total of 40% of the final sample was interviewed directly. The reasons for not obtaining an interview included death (38%), proband refusal (30%), relative refusal (10%), and other (2%). Three or more reports had been obtained from relatives for more than 50% of the adult subjects. In addition, medical records were obtained for more than 60% of the subjects who had been treated for psychological problems, after those patients who had undergone only consultations and brief periods of treatment were excluded. The data were analyzed, with the interview status of the relatives controlled for (Tables 5 and 6).

Diagnostic estimates for adults were made by multiple raters using the modified Research Diagnostic Criteria (RDC). The modified criteria, which have been described previously, primarily involved a greater specification of the criterion of impairment. This was particularly true of the diagnosis of major depression, which requires a minimum of four weeks' duration of symptoms and social or occupational impairment that is noticeable to others in the major role. Each diagnostic category was divided into three levels of diagnostic confidence (definite, probable, and possible). A definite diagnosis was made only if the RDC, in the case of adults, or the DSM-III criteria (for children) were met. A probable diagnosis was made when more than one half of the major criteria were met for a specific diagnostic category. A possible diagnosis was made if at least one major criterion was met.

The diagnostic procedures for the children who were 6 to 17 years of age were somewhat different and are described in detail elsewhere. Information was obtained on children from the probands, their spouses and family members, and medical records. Sixty-four percent of the children had reports from more than one informant. A screening instrument was used to collect data on the symptoms, treatment, and school problems. Information on the reliability between informant reports is presented elsewhere. A best-estimate diagnosis of the children that was based on DSM-III criteria was made by a child psychiatrist who was not involved in the original data collection and who was blind to the clinical status of the proband.

Age of Onset Method and Reliability

The age of onset in both the probands and the relatives was determined by a direct interview (where possible for relatives) and/or family history method from multiple informants, and medical records, when available. A best-estimate approach, made blindly and described elsewhere, was used.

The reliability of the age of onset was examined by comparing the age of onset of depression that was reported in direct interviews and the age that was reported by first-degree relatives, using the family history method. Significant correlations between the direct interview and relatives' reports of the age of onset were obtained for all types of first-degree relatives and spouses (i.e., parents,. siblings, .50; spouses,.50; and offspring older than 18 years,.42). There were no significant differences between the direct interview and relatives' reports in the mean age of onset. The differences in the mean age of onset ranged from 0.8 years for children to 3.8 years for siblings, indicating that the age of onset can be reliably obtained by the family history method.

Statistical Analysis

The following survival-analysis techniques were used to investigate the association between the risk of the age of onset of major depression in relatives and the age of onset of probands.

1. The cumulative survival function and the noncumulative survival function, termed the death-density function, were computed and plotted using life-table methods. The death-density function is derived from the cumulative survival function, and it was found to be particularly appropriate for describing the association between the distribution of the risk of major depression in relatives by the age of onset in relatives and the age of onset in the proband. This function was used, as described by Gross and Clark, to determine the peak period of incidence of major depression in each subset of the population formed by stratifying on the age of onset in the proband.

2. To control simultaneously for all of the potential confounding variables while investigating the effect of the age of onset in the probands on the age-specific incidence risk of major depression in their relatives, the proportional hazard model was used. This model applies the multiple regression method to a survival distribution or another one-time event, such as the onset of a disorder. In the present analysis, a modified form of the proportional hazards model was applied in the manner that has been discussed by Kalbfleisch and Prentice. Because proportional hazard models assume that the underlying hazard functions for the comparison groups are proportional, this model investigates the nonproportionality of the hazard rate that corresponds to the different levels of the age of onset in probands. If the model shows that the hazard rates are not proportional, the hazard function is stratified by the independent variable (which, in this data set, is the age of onset in the proband) and comparisons can be made within each category. However, with this method there is no simple means of testing for the statistical significance between the levels of the stratified variables in the present analysis, the approach used yielded estimates of the cumulative risk of depression for relatives, which were adjusted for potential confounding variables for each category of the age of onset in the probands.

3. One interesting effect in the present analysis was the relationship between the age of onset in the proband and the age of...
onset in the relative. The presence of a statistically significant interaction between the two variables would imply that there is an association between the age of onset of depression in the probands and the age of onset of depression in the relatives. To test for the statistical significance of the interaction between the age of onset in probands and the age of onset in relatives, the data were also analyzed using a log-linear model for the analysis of survivorship that has been proposed by Holford. This model differs from the proportional hazards model in that the follow-up period is divided into discrete intervals rather than being continuous, as in the proportional hazards model. Thus, this model permits one to perform statistical tests of the significance of the effects of covariates on the age-specific incidence within these intervals, even when there is a lack of proportionality of the hazard function across the entire follow-up interval, for the different levels of the covariates of interest.

RESULTS

Age of Onset of Major Depression in Probands, Relatives, and the Community

Table 1 shows the median and mean of the age of onset distributions of major depression in the probands, relatives, and a probability sample drawn from the same community, the New Haven Standard Metropolitan Statistical Area, as part of a large-scale National Institute of Mental Health (NIMH) ECA study of psychiatric disorders in the community. The study methods and details of the community sample are described elsewhere. Data from the ECA are presented on white subjects only, since all of the probands were white. The diagnosis of major depression in the community sample was based on the DSM-III. However, the DSM-III criteria are sufficiently similar to the RDC to allow for comparisons. As shown in Table 1, the relatives and the community sample had an identical median age of onset of 27 years. The median age of onset in probands was only slightly higher—30 years of age.

Overall Rates of Major Depression in Relatives by Age of Onset in Probands

Table 2 shows that there was an inverse linear relationship between the age of onset of major depression in probands and the rates of occurrence of major depression in relatives. The rates of major depression were highest (24.2 of 100) among the relatives of the probands who had the earliest age of onset (<20 years of age). The overall unadjusted rates of major depression were lowest (4.8 of 100) in the relatives of normal subjects. Among depressed probands, the rates were lowest (7.6 of 100) in the relatives of probands who had an onset age of 40 years or older.

Cumulative Risk of Major Depression in Relatives by Age of Onset in Probands

Figure 1 presents the cumulative survival curves for major depression in relatives, stratified by the probands’ age of onset, and again shows that age of onset in probands was inversely related to the rates of major depression in their relatives. The number of subjects who were at risk for each plot is presented in Tables 2 and 4. Probands with an age of onset <20 years had the highest rates of major depression, whereas the relatives of probands with an age of onset of 40+ years had rates of major depression that are slightly higher than the rates in the relatives of normal subjects.

| Table 1.—Age of Onset of Major Depression in Probands, Relatives, and a Community Sample* |
|---------------------------------|---------------|---------------|---------------|
| Age of onset, yr               | Probands     | Relatives     | Community Sample |
| Median                         | 30            | 27            | 27            |
| Mean                           | 32            | 30            | 27            |
| SD                             | 12            | 15            | 10            |
| No. of subjects with major depression | 133          | 150           | 220           |
| No. of subjects                | 215           | 1,518         | 4,437         |
| Diagnostic criteria            | RDC           | RDC           | DSM-III       |

*Data were obtained from the Epidemiologic Catchment Area Study (a probability sample of a community population of adults) conducted in the New Haven, Conn, Standard Metropolitan Statistical Area in 1980 and 1981. All of the subjects were white. RDC indicates Research Diagnostic Criteria.

| Table 2.—Rates of Major Depression in First-degree Relatives of Probands by Age of Onset* |
|---------------------------------|---------------|---------------|---------------|
| Age of onset of major depression, yr | No. of Probands | No. at Risk | Major Depression/100 Subjects |
| <20                             | 18             | 124           | 24.2          |
| 20-29                           | 46             | 314           | 17.5          |
| 30-39                           | 39             | 261           | 11.9          |
| 40-49                           | 30             | 212           | 7.6           |
| Total                           | 215            | 1,518         | ...           |

*All of the subjects were at least 6 years of age.

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Fig. 1.—Cumulative risk of major depression in relatives by age of onset of depression in relatives, stratified by age of onset in proband.
Noncumulative Risk of Major Depression in Relatives
by Age of Onset in Relatives Stratified
by Age of Onset in Probands

Figure 2 presents the noncumulative survival curves to determine the peak period of incidence of major depression in each age-of-onset group of probands and relatives. The values are the risk of major depression per unit of time, estimated at the midpoint of each time interval. Because the width of each of these time intervals is ten years, to compute the risk for a specific time interval these values must be multiplied by ten. For example, 10% of the relatives of probands with an age of onset of <20 years had an age of onset from ages 10 to 19 years. This figure shows the specificity of the transmission of the age of onset. The relatives of probands with the earlier ages of onset were more likely to have early-onset depression as well. Probands with an onset of major depression that occurred before the age of 20 years had relatives with the highest incidence of onset of major depression in the same age group. Probands with an age of onset of depression that was between 20 and 39 years had relatives with the highest incidence of onset between ages 30 to 39 years. The relatives of probands with an age of onset of 40 years or older had rates of early-onset major depression that were similar to the rates in relatives of normal subjects.

Possible Confounding Factors

We have previously shown that many factors (eg, interview status or sex) may confound the results of family studies. Therefore, we undertook a series of analyses to search for possible confounders that might explain the results.

Sociodemographic and Clinical Characteristics.—Table 3 examines the sociodemographic and clinical characteristics by the age of onset in the probands to determine if these characteristics were differentially distributed across the age-of-onset proband groups. The only factors that significantly differed by age of onset were marital status (probands with earlier ages of onset tended to be unmarried at the time of the study) and the number of episodes, which is a possible measure of chronicity (probands with early onset had more episodes). Not shown in Table 3 are the effects of the age of onset, number of episodes, and marital status, which were examined separately. The rates of major depression did not differ among relatives by the number of episodes per proband or by the marital status of probands within the age-of-onset categories. Thus, having either a greater number of episodes or differing marital status did not explain an increased familial aggregation of major depression in the probands who had an early onset of depression.

Effects of Current Age.—Table 4 examines in detail the effect of the current age and shows that the current age of the relative was essentially independent of the age of onset in the proband, ie, relatives were approximately equally distributed across each age-of-onset proband group. Thus, the current age of relatives did not bias the overall results of the life-table curves. Not shown in Table 4 is a similar analysis that examined the current age and the age of onset in the probands. This analysis found that for the probands with ages of onset of <20 years and 20 to 29 years, the current age was not highly correlated with the age of onset (ie, 50% of the probands with an age of onset of <20 years had a current age ≥ 40 years, and 50% of the probands with an age of onset of 20 to 29 years also had a current age of <40 years). The curves for these two ages of onset are the most dramatically different. Thus, the difference cannot be attributed to the confounding by the current age of the proband.

Effect of Generation and Birth Cohort.—An unequal distribution by generation of the relatives by the age of onset in the probands could also have confounded the results. Similarly, if relatives from different birth cohorts were unequally distributed in the various age-of-onset proband groups, this could have confounded the results.

We first examined the distribution of the generations (parents, siblings, offspring) by the age of onset in the probands, and found that, within the proband groups, the subjects were equally distributed by generation. We next examined, within the proband groups, the distribution of the relatives’ generations by the relatives’ birth cohort (defined as a current age of <25 years, 26 to 44 years, or ≥45 years), and found that, by the relatives’ birth cohorts, the generations were distributed equally within the proband groups. (It should be noted that no parents were <25 years of age.) Thus, the generation and birth cohort of the relatives did not appear to be confounding the results.

Family Size.—To determine if a few large families were accounting for the results, we examined the data looking at onset age <20 years of major depression in families rather than in individual relatives by age of onset in probands. Therefore, a family with at least one member with an onset age of <20 years was counted only once. The results again showed specificity of transmission. Fifty percent of the families of probands with onset age of <20 years had at least one family member affected by the onset of major depression at <20 years of age.

This value of 50% was considerably higher than the percent of family members who were affected with an age of early onset of major depression of <20 years in probands with onset ages of 20 to 29, 30 to 39, or 40+ years, and for normal subjects, where the family rates were 24%, 13%, 10%, and 5%, respectively.

Effects of Assortative Mating.—The high degree of assortative mating among depressed patients could also have confounded the results. Our own and other studies have shown that assortative mating in parents markedly increases the risk of major depression in children. Whereas a high degree of concordance for depression was observed among the depressed probands and their spouses in the present study, only one concordant couple for...
depression was found among the parents of probands. Thus, an increased risk of depression among the siblings of probands cannot be attributed to assortative mating in the parental generation.

To determine whether assortative mating was confounding the results of the present analysis, the offspring of probands were excluded and the previously described life-table analyses were conducted for parents and siblings of probands only. The results (not illustrated herein) were essentially the same as those shown in Figs 1 and 2. Assortative mating had not biased the overall results of the life-table analysis.

**Risk of Major Depression Among Relatives by Age of Onset in Probands, Controlling for Current Age and Sex of Proband and Relative and Interview Status**

Table 5 shows the relative risks of depression among relatives of the various age-of-onset proband groups compared with the relatives of normal subjects. These relative risks, or ratios of proportions, are adjusted for the effects of the current age and sex of the proband and his or her relative, and the interview status (whether the data on relatives were collected by interview or by family history) by the Kalbfleisch and Prentice method that was previously described.

Even after controlling for the five possible confounders, probands with an age of onset of <20 years had a risk of having a relative with an age of onset <20 years that was 7.78 times higher than the risk in the relatives of normal subjects.

There was another peak (a fivefold increase) in relatives with an age of onset of 40 to 49 years.

The risk of having a relative with onset at <20 years decreased linearly as the age of onset in the probands increased, from more than a threefold increase in risk of the relatives of probands with onset ages of 20 to 29 years to more than a twofold increase in risk in the relatives of probands with onset ages of 30 years or older. Similar trends were found in the relatives who had onset ages of 20 to 29 years. The greatest increase in the risk of having relatives with onset ages of 30 to 39 years (approximately fourfold) was in probands with onset ages of 20 to 29 years.

The least increase in risk was in relatives with onset ages of 50 years and older, regardless of the onset age in the proband, and in the probands with onset ages of 40 years and older, regardless of the onset age in the relatives. These findings again suggest that an older age of onset of major depression, whether in probands or relatives, has lower familial loading than an onset that occurs at earlier ages. Overall, the risk of major depression in the relatives of probands with onset of major depression before the age of 20 years was 3.27 times greater than in normal subjects, and, in probands with an onset age of at least 40 years, was only 1.62 times greater than in normal subjects.

**Significance of the Effects of the Age-Specific Incidence of Major Depression in Relatives**

The results of the log-linear analysis of age-specific incidence rates of major depression in relatives by the age of onset in the proband, the age of onset in relatives, sex, and the interview status
are shown in Table 6.

There was a significant main effect of the age of onset in both the probands and the relatives. Proband and relatives with the earliest age of onset had the highest rates of major depression. As has been found previously, there was a sex effect, with female relatives having significantly higher rates of major depression than male relatives, and a strong interview effect, with interviewed relatives having higher rates of major depression than noninterviewed relatives. There was a significant interaction between the age of onset in the proband and the age of onset in the relative. Probands with an onset age of <20 years had significantly higher rates of relatives with onset <age 20 years. There was no significant interaction between sex and the interview status.

**COMMENT**

Following is a summary of our findings. 

1. We found an inverse linear relationship between the rates of major depression among relatives and the age of onset of major depression in the probands. First-degree relatives of probands who had an age of onset of major depression that was younger than 20 years had the highest risk of major depression in their first-degree relatives.

2. There was specificity of transmission of the age of onset of major depression between probands with earlier ages of onset and their relatives. The relatives of probands who had an age of onset of depression that was younger than 20 years had a nearly eightfold risk of having an onset of major depression prior to the age of 20 years, compared with the relatives of normal subjects.

3. There were only slightly elevated rates of major depression in the relatives of probands with later ages of onset (>40 years) of depression when they were compared with the relatives of normal subjects or with the relatives of probands with earlier ages of onset.

4. The results were not confounded by the effects of sex or the current age of the probands or of the relatives, the marital status or chronicity of the probands' disorders, an unequal distribution of the generations of relatives, the birth cohorts of the relatives, assortative mating for depression between probands and their spouses, family size, or the interview status of the relatives.

5. The median age of onset of major depression was similar among probands, relatives, and a sample of subjects that was drawn from the same community.

These findings and their implications for understanding previous family studies and for planning future studies should be viewed in light of the converging evidence for the onset of some types of major depression in children and adolescents, for the association of these early-onset depressions with high familial loading, and for specificity of transmission.

**Early-Onset Major Depression: Epidemiologic Evidence**

The age of onset, an important source of heterogeneity in major depression, has been reported in many family studies. Most studies have found an increased risk of depression among the relatives of probands with early <i>v</i> late onset. However, these family studies, with the exception of studies by Gershon et al and Angst, have divided early and late onset at approximately 40 years of age. Our data suggest that the highest familial loading is in probands with onset age of <20 years, and that considerable information about diagnostic heterogeneity may be gained by the closer examination of probands who have onset ages of <20 years. The use of the age of 40 years to divide early- and late-onset depression follows the commonly held view that major depression is a disorder of the middle-aged and the elderly, and that it does not occur in children and rarely occurs in adolescents. This view has been increasingly challenged by the results of epidemiologic studies; eg, Kashani et al, in a general population study of 956 9-year-old children who were born in 1972 and 1973 in the Dunedin area of New Zealand, used the Kiddie-Schedule for Affective Disorders Schizophrenia—Epidemiologic Version and RDC and found current point prevalences of major and minor depression that were 1.8% and 2.5%, respectively.

Examining a probability sample of more than 9,000 adults (18 years of age and older) from three urban communities (New Haven, Conn, St Louis, and Baltimore) in the ECA study, Myers et al found that the highest six-month prevalence rate of major depression (DSM-III) was in the 18- to 44-year-old age group. In the same study, Robins et al reported that the lifetime rates of major depression also were highest in the younger age group. Weissman and Myers reported similar findings in their 1978 survey of New Haven.

Weissman et al, who also participated in the ECA study, noted Klerman's earlier suggestion of a post-WW II cohort effect for major depression; they examined the age of onset of major depression by birth cohort and found that the cohort that came to maturity following WW II (born after 1936) had the earliest onset age and the highest rates of major depression. Identical findings were first reported by Klerman et al, based on the examination of approximately 2,400 interviewed, first-degree relatives in the Family Study of Affective Disorders from the NIMH Collaborative Study of the Psychobiology of Depression.

While it is not clear if the cohort effect is real or is due to reporting, memory, or selective survival, a recent study by Hagnell et al had suggested that the increase in the rates of depression in young adults and the early onset, may be real. Using a different design and community, Hagnell et al reported on the Lundby cohort from Sweden that had been studied since 1947, and found a marked increase in mild to moderate major depression during a 25-year period, especially in subjects <30 years of age. This increase could not be explained by changing diagnostic criteria, memory, or reporting. Recent studies have also suggested that symptom patterns and the course of major depression in younger age groups are similar to those of adults. In summary, there is a marked consistency in the finding, using different designs and places, of a high and increasing rate of depression among young persons.

**Early-Onset Major Depression: Family Studies**

Our finding that probands with the earliest age of onset of major depression may have the most severe forms, in terms of the highest familial loading, are consistent with recent family studies that have defined the depressed child as the proband and have examined the child's family. Puig-Antich et al studied the families of ninety-five 6- to 12-year-old children who had RDC-diagnosed endogenous or nonendogenous major depression, compared with nondepressed, emotionally disturbed children and children who had never been mentally ill. They found that the first-degree relatives of children with endogenous or nonendogenous major depression were significantly more at risk for the development of major depression than were the relatives of the children of normal subjects or children with other psychiatric disorders. Fifty percent of the first-degree relatives of prepubertal children with major depression had at least some depressive disorder. A finding of similar high rates of major depression in the adult relatives of adolescent probands with either unipolar or bipolar illness was found by Strober et al.
Studies that define the child or adolescent as the depressed proband and examine the rates of illness in adult relatives may tend to find very high rates because of treatment bias, eg, parents with psychiatric illness themselves may be more inclined to bring their ill children for treatment and then enter them into a study. However, the studies by Puig-Antich et al and Strober et al have used control groups in which the same treatment bias was operating, and they have shown differences in rates between the families of depressed children and control subjects. In these studies, as well as in others, the absolute risk in relatives was not as meaningful as was the magnitude of the differences in families of patients and control subjects.

It should be noted, however, that Gershon et al did not find a relationship between morbid risk in relatives and the age of onset (defined as being either <30 or <40 years of age) in probands. However, in their study, the major affective disorders in both the probands and the relatives were pooled (including schizoaffective, bipolar I and II, and unipolar disorders) and were not examined separately.

The age-of-onset heterogeneity appears to be limited to cases that are defined by major depressive disorder in the proband. When the proband was defined as having bipolar affective disorder, our collaborators at the NIMH, using substantially the same methods of family study, found no evidence for an increased prevalence in the relatives of patients with a younger age of onset. In 505 relatives of 89 probands, the rate of major depression per 100 relatives (as previously defined) was 13.2, 8.2, 14.8, and 10.5 for probands with onset ages <20, 20 to 29, 30 to 39, and at least 40 years, respectively. Also, our collaborators did not find an increased risk of major depression in the 6- to 17-year-old children of the bipolar probands when they were compared with the children of normal control subjects (oral communication, E. S. Gershon, MD, April 1984).

It was not possible to test the findings on the age of onset with the probands with nonbipolar illness in the NIMH data because that sample included only 30 probands with major depression. When these probands were divided by the age of onset, only eight had onset ages of <20 years, eight had onset ages of 20 to 29 years, nine had onset ages of 30 to 39 years, and five had onset ages of ≥40 years. Therefore, there were too few subjects to allow any comparable analysis with controls for cohort, sex, interview status, etc. Probands with bipolar disorder, and possibly some patients with nonbipolar disorder, may have a maximal prevalence of affective illness in relatives, which is not further affected by the factors that lead to early onset.

**Research Implications**

The specificity of the transmission of the onset of major depression before the age of 20 years supports the validity of this age-of-onset distinction as a severity factor and source of heterogeneity in major depression.

Taken together, the data suggest that it may be useful to redefine the early onset of major depression in biologic and family studies as an onset age of <20 or 30 years, and not as an onset age of <40 years. It may also be useful to study patients who have onset ages of <20 years who also have relatives with early-onset disorder. Our results also suggest that biologic studies of children and adolescents who have affective disorders may provide a promising future direction for research. Moreover, some onset age 40 and older may not be familial. Biologic studies should separate this late-onset group. Most biologic studies of major depression are conducted in hospitalized patients and, since hospitalized depressed patients tend to be older and are more likely to have a later onset of depression, the inclusion of these older patients who have a later onset may obscure the findings.

**Sources of Heterogeneity of the Early-Onset Probands**

Early-onset major depression may still be heterogeneous. Our data do not preclude the presence of more than one early-onset affective disorder such as early-onset affective disorder with anxiety disorder or with a delusional subtype. A future analysis of these data that looks at the different subtypes of major depression and/or comorbidity in the probands with early onset will examine this issue.

**Survival Time Models With Proportional Hazards Functions**

The statistical approach used in this study combined the use of survival curves, a modification of Cox's proportional hazards model, and log-linear models. The approach unites two different fields (survival- and contingency-table analysis) in a single analytic framework based on the log-linear model.

While survival curves (life-tables) and proportional hazards analysis are being used with increasing frequency for psychiatric data, the use of log-linear models that use survivorship data with covariates has not, to our knowledge, been used in family studies of psychiatric disorder. This method, described in 1980 by Hollard and applied by him to data on survivors of lung cancer (testing for interactions with the histology and stage of disease), is well suited for large data sets from family studies. It is valuable when, as is often the case in family studies, there are many groups and/or covariates and few subjects in each group. The analysis can test for group differences in survival. Once a satisfactory model is found, the expected values of the outcome (ie, the fitted table) can be used as numerators in the standard actuarial analysis to give smoothed life-tables for each group. An additional advantage is that the data can be handled by using, without modifications, existing computer packages that have been developed for the log-linear analysis of contingency table data to provide estimates and tests for survival data and life-tables.

Applied to the data presented in this report, we divided the survivorship time into discrete intervals (years in decades) and tested for the interactions between the age of onset of major depression in probands and in their relatives, while controlling for the effects of the covariates (the age and sex of the relative and proband, the interview status, etc) within each discrete age interval. Using this method, we found the significant interaction term between an age of onset of major depression <20 years in probands and in their relatives, after controlling for the effects of the covariates.

**Separating Cohort From Family Effects**

While we showed that high familial loading was associated with the early onset of depression, even when we controlled for the cohort effects, there was a need to reconcile the high familial loading of early-onset depression with the apparent secular changes in the rates of major depression and the cohort effects that were found in recent epidemiologic studies. These secular changes suggest that environmental forces may have an impact. There may be two processes (a birth cohort and an age-of-onset effect) that could confound family studies. Future family studies will need to control for both processes to sort out gene-environment interactions. However, a family study design cannot readily separate cultural from genetic transmission.

Our findings confirm that the emerging picture of affec-
tive illness is different from the classic view. A very early onset of major depression is much more common than was previously believed, and this represents the most severe form in terms of familial loading. These findings in family studies need to be reconciled with the apparent recent secular changes in major depression in the age cohort that came to maturity after WW II. Parallels of these findings in major depression can be found in other chronic diseases. For example, the seemingly contradictory findings for major depression (secular changes, a birth cohort effect, and a family effect) can be found in some forms of cancer.46 An early age of onset of a disorder as a severity factor and as a source of heterogeneity is also found in diabetes.60

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