

Evidence for Comorbidity of Anxiety and Depression: Family and Genetic Studies of Children

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THE FOCUS OF this chapter is on evidence for comorbidity of depression and anxiety disorders in children. The evidence is based primarily on data from family-genetic studies. The purpose is to clarify the relationship between these disorders. Are anxiety and depression etiologically the same disorder with different clinical features? Are they on a continuum of severity? Or are they etiologically different disorders with an overlap in clinical features?

The specific questions relevant to these questions in studying children using family-genetic approaches are: (1) do depression and anxiety disorders transmit between parents and children; (2) do they co-occur within children; and (3) do they continue from childhood to adulthood?

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Inclusion of studies on children in a book on comorbidity of mood and anxiety disorders is quite appropriate because there is increasing evidence that depression and anxiety disorders do occur in children, that the mean age of onset of these disorders is usually in adolescence or young adulthood, and that early onset depressions have high familial loading (Weissman, Wickramaratne, Merikangas, et al. 1984).

Children usually have been excluded from family-genetic, twin, and cross-fostering studies, in part due to real diagnostic problems in their assessment and in part due to the belief that depression did not occur in children. Moreover, most family-genetic studies have originated in adult psychiatry, and there has been less interest in studying children. This situation is changing, and data on the rates and nature of depression and anxiety disorders in children are now becoming available.

DEFINITION OF CHILDREN

Any discussion of psychiatric disorders in children should define what is meant by "children," which is an awkward classification. It can refer to a class of biologic relatives (offspring), to sons or daughters, or to a youthful age group. In family-genetic studies, *children* usually refers to the probands' adult offspring over age 17 years, since younger children have usually not been included in these studies. In this chapter, I will focus on children as the offspring of a proband and as a youthful age group. Data will be presented on minor children, usually ages 6 to 17 years, although the age range varies somewhat in the data presented.

DIAGNOSTIC CLASSIFICATION OF CHILDREN

Anxiety Disorders

Anxiety disorders in the third edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-III) (America Psychiatric Association 1980) have been separated into subtypes for adults and for children. Those anxiety disorders first evident in childhood and adolescence include separation anxiety, avoidant disorder, and overanxious disorder. For adults, anxiety disorders include panic disorder, agoraphobia with and without panic attacks, social phobia, simple phobia, generalized anxiety disorder, obsessive-compulsive disorder, and posttraumatic stress disorder. Although DSM-III includes a separate category of anxiety disorders having their origins in infancy and childhood, except for the explicit requirement that generalized anxi-

ety disorder cannot be diagnosed before age 18, there is no contraindication to diagnosing the other adult anxiety disorders in children.

The revision of the DSM-III, DSM-III-R (American Psychiatric Association 1987), includes some modifications in the anxiety disorders. However, the disorders first evident in childhood do not differ from DSM-III. There is some reclassification of the adult anxiety disorders. Agoraphobia is now a separate disorder. As before, the adult classifications can be applied to children. In DSM-III-R, it is permissible to diagnose generalized anxiety disorder in children.

Depression

In both DSM-III and DSM-III-R, there is no separate category for depression disorders first evident in infancy or childhood. All the adult disorders can be classified in childhood. There are minor criteria changes when used in children. For example, irritability can substitute for depressed mood in children and adolescents. Failure to make expected weight gains can substitute for weight loss. One (not 2) years' duration is required for the diagnosis of cyclothymia or dysthymia in children. Although there are minor differences in the ordering of affective disorders, and they are called mood disorders in DSM-III-R, these changes should not substantially change future considerations of depression or anxiety disorders in children.

There are no published studies on children using DSM-III-R criteria, and only a few are available using DSM-III. For this chapter, most of the diagnoses are based on DSM-III.

DO DEPRESSION AND ANXIETY DISORDERS TRANSMIT BETWEEN THE GENERATIONS?

Research Strategies

Although family-genetic studies do not yield evidence for the amount of genetic variance contributing to a disorder, the data can provide better understanding of diagnostic heterogeneity. It is quite likely that many of the psychiatric disorders are groups of conditions rather than single entities with different etiologic and modifying risk factors. The use of family data in the absence of specific neuropathologic evidence is one approach to identifying homogeneous diagnostic subgroups. If the diagnostic subgroup under study increases risk of the disorder and "breeds true" within families, potential evidence for the validity of the diagnostic group is suggested. If adult forms of a disorder are related to increased risk of specific disorders in their offspring, this suggests a relationship between the adult and childhood disorders.

Because variation in expression of a particular trait within families is assumed to result from the same latent factor, family studies can yield information on variable expressivity of the gene or genes related to the phenotypic trait. This property of family studies can lead to the development of more precise clinical descriptions of the full spectrum of disorders. Studies of the young children of adult probands can yield information on the transmission of disorders and/or symptoms across generations, on the early signs and childhood forms of the disorder, and on the risk or protective factors that mediate the development of the disorder.

Between-generation studies to determine the relationship of one disorder to another raise questions about the risk of the child's disorder vis-à-vis the parents' diagnoses. For example, if children of parents with depression have increased risk of both depression and anxiety disorder or if children of parents with anxiety disorder have increased risk of both depression and anxiety disorder, this would suggest that anxiety and depression are similar disorders. Alternately, if children of depressed parents have increased risk of depression, but not of anxiety disorder, this would suggest that depression and anxiety are separate disorders. If parents with anxiety disorder have children with increased risk of anxiety disorder and not depression, this would strengthen the theory.

Case-Control Studies

There are several designs for family-genetic studies, and they yield somewhat different information. The case-control design is the most commonly used. A more complete assessment of the design used in family studies can be found in Weissman, Merikangas, John, et al. (1986). With a case-control design, a proband with the illness under investigation is selected for study and is then matched to a control proband (i.e., an individual who does not have the illness under investigation but who is comparable on other characteristics).

Usually the prevalence of the condition among first-degree relatives of the proband is compared to prevalence among the first-degree relatives of controls. In the absence of control groups, the rates of illness among relatives can be compared to population rates. This design requires accurate information on population at risk. In either case, these studies usually have a retrospective cohort design in that the lifetime rates of illness in relatives are obtained on the basis of recall of their lifetime incidence of disorders. As noted before, children under the age of 18 years have traditionally been excluded from these studies.

Top-Down Studies

In family studies of psychiatric disorders, the probands or index cases with the disorder being investigated have nearly always been adults who were selected from treatment settings or from psychiatric or case registries. Family studies which begin with the adult probands and their spouses, and study psychopathology among their offspring as well as other relatives, have been termed *top-down* studies by Puig-Antich (1980).

Bottom-Up Studies

With the increasing interest in childhood psychiatric disorders during the last decade, children have also begun to be defined as the probands in family studies, termed by Puig-Antich (1980) as *bottom-up* studies. Similar to the adult studies, children who serve as probands generally have been selected from treatment settings. Studies that begin with the child or adolescent as the proband, or index case, tend to find very high rates of illness in the child's adult relatives, possibly because of sampling bias. Although the proband is the treated child, it is the parent who brings the child for treatment and who grants permission for the child to be included in the study. Ill parents, or parents sensitized to the effects of the illness because of having several ill family members, may be more likely than well parents to bring their children to treatment and to consent to the child's inclusion in the study.

One method used to control for this ascertainment bias has been to select a comparison control proband group of children with another treated psychiatric illness. The rates of all types of psychiatric illness will also tend to be high in the adult relatives of the child comparison group. However, the types of illness and the magnitudes of the differences in rates between the relatives of the cases and the relatives of the comparison control group can provide more important information than the absolute rates of illness in the relatives.

High-Risk Studies

The high-risk paradigm is a variant of the case-control and the top-down family study (Garmezy and Streitman 1974). The focus is usually limited to the young offspring of ill probands. The proband is a parent. Usually there is no assessment of the proband's first-degree or other relatives, although such an assessment is quite important in understanding transmission of disorders to offspring. In high-risk studies, the offspring are usually studied longitudinally to identify

risk factors that are premorbid to, rather than concomitant with, the first onset of the disorder. Such factors may serve to identify vulnerable individuals and permit efforts toward prevention and intervention.

The high-risk design studies have yielded the most data relevant to the topic of transmission of specific disorders between the generations. Data primarily on depressive disorders are now becoming available from these studies.

Evidence From High-Risk Studies

Orvaschel (1983) and Beardslee, Bemporad, Keller, et al. (1983) independently published excellent scholarly reviews of the status of research on parental depression and child psychopathology and reached similar conclusions. Most of the studies included fewer than 40 children and produced a wide range in rates, which the authors attributed to methodological differences between studies. The studies varied by informant (child about self or parent about child); by diagnostic method (symptoms scale or diagnostic interview); by diagnostic criteria; by methods of calculating rates (the family unit or the number of children affected); and by type of affective illness in the parent (unipolar or bipolar).

Although the methodological limitations of the studies conducted at that time were considerable, the findings all pointed in the same direction. The children of affectively ill parents were at a significant risk for developing psychopathology, particularly depression.

Since the publication of these reviews, the methodology of children's studies has improved considerably. There are now at least seven well-designed studies that include children (ages 4 years and older) of parents with major depression or anxiety disorders (see Table 1). Many of these studies are ongoing and have only recently begun to yield data (Breslau, Davis, and Prabucki 1987; Hammen, Gordon, Burge, et al. 1987; Kagan, Reznick, Snidman, et al. 1988; Keller, Beardslee, Dorer, et al. 1986; Orvaschel, Walsh-Allis, and Ye 1988; Sylvester, Hyde, and Reichler 1988; Weissman, Gammon, John, et al. 1987).

More than 350 offspring of depressed parents, 150 offspring of anxious parents, and 400 offspring of controls have been studied. A variety of control groups have been included, most commonly the children of parents never psychiatrically ill. However, children of bipolar and of medically ill parents have also been studied. All these studies have included a structured diagnostic interview of children: Kiddie Schedule for Affective Disorders and Schizophrenia (K-SADS), Diagnostic Interview Schedule for Children (DISC), or Diagnostic

Table 1. Characteristics of Recent High-Risk Studies of Children of Parents With Major Depression and/or Anxiety

Study	Study children		Control children		Ages of children (years)	Diagnostic instrument	Family information	Follow-up
	Parent diagnoses	N	Parent diagnoses	N				
Orvaschel, Walsh-Allis, and Ye (1988)	≥ 1 parent MDD	61	Neither parent ill	45	6-17	K-SADS	History 1st- & 2nd-degree relatives	18 months
Keller, Beardslee, Dorer, et al. (1986)	≥ 1 parent MDD	72	Neither parent ill	24	6-19	DICA	History & interview 1st- & 2nd-degree relatives	No
Hammen, Gordon, Burge, et al. (1987)	≥ 1 parent MDD	19	≥ 1 parent BP	12	8-16	K-SADS	Interview both parents	6 months for 3 years
			≥ 1 parent CMI	18				
			Neither parent ill	35				
Weissman, Gammon, John, et al. (1987)	≥ 1 parent MDD	153	Neither parent ill	67	6-23	K-SADS	History 1st- & 2nd-degree relatives	2 years
Breslau, Davis, and Prabucki (1987)	Mother GAD Mother MDD	101 56	Mother not ill	174	8-23	DISC	Interview mother	No
Sylvester, Hyde, and Reichler (1988)	≥ 1 parent panic	50	Neither parent ill	48	7-17	DICA	No	Yes
	≥ 1 parent MDD	27						
Kagan, Reznick, Snidman, et al. (1988)	≥ 1 parent panic	18	Other problems	14	4-7	Direct observation	Interview both parents	No

Note. All studies but Breslau, Davis, and Prabucki used consensus diagnosis. MDD = major depression; BP = bipolar disorder; CMI = chronic medical illness; GAD = generalized anxiety disorder; K-SADS = Kiddie Schedule for Affective Disorders and Schizophrenia; DICA = Diagnostic Interview for Children and Adolescents; DISC = Diagnostic Interview Schedule for Children.

Interview for Children and Adolescents (DICA) (for a review, see Weissman, Merikangas, John, et al. 1986). At least one parent was interviewed. Diagnoses of children were made blindly as to their parents' clinical status. DSM-III criteria were used for the children. Consensus diagnosis was made on all available data.

In all but three studies (Breslau, Davis, and Prabucki 1987; Hammen, Gordon, Burge, et al. 1987; Sylvester, Hyde, and Reichler 1988), family history is available on the child's first- and second-degree relatives, and attention has been paid to the spouse's diagnosis. Four of the studies (Hammen, Gordon, Burge, et al. 1987; Orvaschel 1986; Sylvester, Hyde, and Reichler 1988; Weissman, Gammon, John, et al. 1987) include a follow-up assessment.

The study by Breslau, Davis, and Prabucki (1987) was not designed specifically to estimate familial aggregation of psychiatric disorders, but rather to determine child disability and its effect on families. This study provides some information on relative risk of psychiatric illness in children of depressed mothers. However, because only annual, and not lifetime, prevalence is reported in the Breslau, Davis, and Prabucki investigation, rates are not directly comparable with the other studies.

All of the studies confirm earlier reports that offspring of depressed and of anxious parents are at increased risk of major depression as well as anxiety disorders. A range of diagnoses in children are represented. The rates of any diagnosis in children are quite high and, in studies reporting these data, range from 41.0 to 75.9 per 100 for children of parents with major depression (Table 2).

In children of depressed parents, both major depression and anxiety disorders are transmitted to the children in nearly equal frequency (Table 2). This is also true in the two high-risk studies of the children of parents with panic disorder or generalized anxiety disorder (Table 3). The rates of depression or of anxiety disorders in children of depressed or anxious parents are considerably higher than in children of parents with no psychiatric illness (Table 4).

The range of rates of major depression in children of depressed parents between studies is still wide (15 to 41 per 100), although these variations are not nearly as great as in previous studies (Table 2). The lowest rates in children derive from the Orvaschel (1986) study. As noted before, in the Breslau, Davis, and Prabucki (1987) study, only annual rates of illness are reported, and the parents are mildly ill subjects drawn from a community sample. The highest rates are from the Hammen, Gordon, Burge, et al. (1987) study, which included only 19 children whose mothers had chronic and recurrent depression. Keller, Beardslee, Dorer, et al. (1986) showed that chronicity of depression in parents increased the risk of the disorder in their children.

Table 2. Rates (per 100) of Psychiatric Illness in Children of Parents With Major Depression

Study	Diagnoses in children		
	Major depression	Any anxiety disorder	Any disorder
Keller, Beardslee, Dorer, et al. (1986)	24.0	16.0	65.0
Orvaschel, Walsh-Allis, and Ye (1988)	15.0	20.0	41.0
Hammen, Gordon, Burge, et al. (1987)	41.0	21.0	74.0
Breslau, Davis, and Prabucki (1987)	16.0	21.0	—
Weissman, Gammon, John, et al. (1987)	28.1	39.9	75.9
Sylvester, Hyde, and Reichler (1988)	37.0	44.0	—

Note. All rates are lifetime, except Breslau, Davis, and Prabucki, which are annual.

Table 3. Rates (per 100) of Psychiatric Illness in Children of Parents With Anxiety Disorder

Study	Diagnoses in parent	Diagnoses in children	
		Major depression	Any anxiety disorder
Sylvester, Hyde, and Reichler (1988) ^a	Panic	48.0	42.0
Breslau, Davis, and Prabucki (1987) ^b	GAD	11.0	11.0 (GAD) 9.0 (SAD)

Note. GAD = generalized anxiety disorder; SAD = separation anxiety disorder.

^aLifetime rates.

^bAnnual rates.

There has been one quite interesting study of the young children (ages 4 to 7 years) of probands with panic disorders using direct observational techniques and a developmental perspective (Kagan, Reznick, Snidman, et al. 1988) (Table 1). Based on observation made

Table 4. Lifetime Rates (per 100) of Psychiatric Illness in Children of Parents With No Psychiatric Disorder

Study	Diagnoses in children	
	Depression	Any anxiety disorder
Sylvester, Hyde, and Reichler (1988)	9.0	3.0
Weissman, Gammon, John, et al. (1987)	13.4	17.9
Hammen, Gordon, Burge, et al. (1987)	9.0	12.0*

*Separation anxiety and overanxious disorders.

blindly as to the parental diagnosis, the investigators found that the children of panic probands, as compared to children of controls, were more inhibited behaviorally, were more reluctant to talk to an unfamiliar but friendly examiner, and (in this situation) showed a trend toward sympathetic activation and cognitive stress, as reflected in increased heart rate and cortisol levels. This study suggested that anxiety symptoms may be apparent in the very young offspring of probands with panic disorder. No data on childhood depression are presented.

Evidence From Bottom-Up Studies

The three bottom-up studies (i.e., those that select the child as the proband and examine rates of illness in the child's first-degree relatives) confirm the previous findings about the relationship between depression and anxiety. Puig-Antich and Rabinovich (1986) examined major depression in the relatives of children with major depression, with and without separation anxiety, as well as children with separation anxiety without major depression (Table 5). They found equally high rates of major depression in their adult relatives and no significant difference in rates of depression by proband group.

Table 5. Lifetime Risk (per 100) of Major Depression in Adult Relatives of Children With Depression and/or Anxiety Disorders

	Diagnosis in children		
	Major depression with separation anxiety (N = 28)	Major depression without separation anxiety (N = 19)	Separation anxiety without major depression (N = 12)
Major depressive disorder first-degree relatives	43	55	39

Note. Recalculated from data presented in Puig-Antich and Rabinovich (1986).

A second bottom-up family study of 127 relatives of 4 children with overanxious disorder, 8 with separation anxiety, and 11 with major depression found similar rates of major depression in the children's relatives (Livingston, Nugent, Rader, et al. 1985) (Table 6). The rates of panic disorder were elevated in the adult relatives of anxious children. However, it was unclear how many of the children's first- or second-degree relatives were actually assessed in this study. It should be noted that the diagnosis of adult relatives was only by family history. The family history methods usually tend to underestimate illness in relatives.

Table 6. Lifetime Rates (per 100) of Depression and Anxiety Disorders in the Adult Relatives of Children With Depression or Anxiety Disorders

Diagnoses in adult relatives*	Diagnoses in children	
	Major depression (<i>N</i> = 11)	Separation anxiety or overanxious disorder (<i>N</i> = 12)
Major depression	15.5	14.5
Generalized anxiety	5.2	—
Panic	—	11.6

Note. Derived from Livingston, Nugent, Rader, et al. (1985).

*Diagnoses by family history in parents, grandparents, aunts, uncles, or siblings.

In the third study, Last, Francis, Hersen, et al. (1987) found extremely high rates of anxiety disorders and major depression in the mothers of 19 children (ages 6 to 17 years) with separation anxiety and 22 with overanxious disorder, as compared to a control group of children with other psychiatric disorders (Table 7). Taken together, these studies in children suggest that depression and anxiety disorders transmit across the generation and are interchangeable.

Table 7. Lifetime Rates (per 100) of Anxiety and Major Depression in Mothers of Children With Anxiety Disorders

Diagnoses in mothers	Diagnoses in children		
	Separation anxiety (<i>N</i> = 19)	Overanxious disorder (<i>N</i> = 22)	Controls (<i>N</i> = 15)
Any anxiety disorder	68.4	86.4	40.0
Major depression	52.6	31.8	26.7

Note. Derived from Last, Francis, Hersen, et al. (1987).

DO DEPRESSIVE AND ANXIETY DISORDERS CO-OCCUR IN CHILDREN?

Understanding the co-occurrence of disorders is useful for clarifying diagnostic problems in transmission, but does not yield much information on the discreteness of disorders unless information on chronology and stability can be obtained. In general, the studies of children on co-occurrence of depression and anxiety report findings similar to those reported in studies of adults. There is a high co-occurrence; chronology is difficult to ascertain but occurs probably equally. In adults, a high co-occurrence of depression, anxiety, and alcohol disorder is reported. In studies of young children, conduct disorder is substituted for alcohol abuse. In older children, both drug and alcohol abuse is reported.

Six studies of children using modern diagnostic criteria report data on the co-occurrence of depression and anxiety disorders in children (Table 8). The studies vary by the type of anxiety or affective disorder studied.

Table 8. Co-Occurrence of Affective and Anxiety Disorders in Children

Study	Diagnoses in children	Comorbid disorder	%
Kovacs, Feinberg, Crouse-Novak, et al. (1984a, 1984b)	Major depression	Anxiety disorder	33
Kashani, Beck, Hooper, et al. (1987); Kashani, Carlson, Beck, et al. (1987)	Major depression	Anxiety disorder	75
Weissman, Gammon, John, et al. (1987)	Major depression	Anxiety disorder	55
Puig-Antich (1987)	Major depression	Phobia	48
Puig-Antich (1987)	Major depression	Separation anxiety	59
Bernstein and Garfinkel (1986)	Phobia	Affective disorder	69
Last, Francis, Hersen, et al. (1987)	Phobia	Affective disorder	33

Kovacs and colleagues (Kovacs, Feinberg, Crouse-Novak, et al. 1984a, 1984b) investigated 65 adolescents (ages 8 to 13 years) receiving treatment for a depressive disorder and found high rates of coexisting disorders. Of the children with major depression, 33% had coexisting anxiety disorder. Information on chronology was not available from the cross-sectional data, although the authors felt that the chronology of the other disorders simultaneously or secondarily were equally likely for all but dysthymia, where the early age of onset usually

predated the other disorders. Presence of a concomitant anxiety disorder over a 6-year period did not influence remission from or relapse into a new depressive episode.

In a community survey study of 150 adolescents (ages 14 to 16 years) attending public school, Kashani and colleagues (Kashani, Beck, Hooper, et al. 1987; Kashani, Carlson, Beck, et al. 1987) found that 41.3% had at least one DSM-III disorder. Anxiety, depression, and conduct disorders were the most common. There was high comorbidity between these disorders. Of the 150 adolescents with major depression, 75% had additional diagnoses of anxiety disorders.

In a study of 220 children (ages 6 to 63 years) of depressed and normal parents, Weissman, Gammon, John, et al. (1987) found that 55% of 220 children with major depression had comorbid anxiety disorders.

In a study of 80 prepubertal children with major depression, Puig-Antich (1987) found that 48% had co-occurring phobias; 59%, separation anxiety; and 11%, obsessive-compulsive disorder.

Bernstein and Garfinkel (1986) studied 26 young adolescents with school phobia. They found that 69% met DSM-III criteria for major depression. Children with depression frequently reported anxiety; those with anxiety did not commonly describe major depression, except where the anxiety was severe. In a study of 67 children with separation anxiety (mean age, 9 years) or school phobia (mean age, 14 years), Last, Francis, Hersen, et al. (1987) found that 50% of the children had another anxiety disorder and about 33% had an affective disorder.

DO THE CHILDHOOD DISORDERS CONTINUE INTO ADULTHOOD?

Longitudinal studies, whether or not part of a high-risk design, can yield information on comorbidity. Evidence that there is continuity of a childhood disorder (either anxiety or depression) into adulthood and that disorders are not interchangeable strengthens the evidence for the separation of the disorders. Evidence that the disorders are interchangeable between childhood and adulthood would suggest that they are similar disorders with different manifestations at different ages.

As of this writing, there has not been one published longitudinal study of individuals, first identified as having an anxiety or depressive disorder in childhood, who have been followed to adulthood to determine the natural history, clinical course, or prognostic significance of these childhood disorders and their continuity to the adult disorders. One such study for separation anxiety has just been under-

taken by Gittelman-Klein at Columbia University; others for a range of depressive disorders are underway by Kovacs at the University of Pittsburgh and by Rutter at The Maudsley Hospital in London.

Information is available on shorter-term follow-up of children and of retrospective accounts of the childhood of adult patients. In regard to depression, Kovacs, Feinberg, Crouse-Novak, et al. (1984a) studied 65 prepubertal depressed children over 6 years and showed that there is continuity of this disorder. Kandel and Davies (1982, 1986) identified 1,000 15- and 16-year-olds with depressed mood from a high school survey and followed them over 9 years. These investigators found continuity of depressive symptoms (particularly in girls) and high rates of associated social and interpersonal morbidity and drug use. Similar conclusions were reached by Poznanski, Krahen-guhl, and Zrull (1976) in a study of 10 youths (mean age, 16.9 years) over 6½ years. They found that 50% of the children were clinically depressed 6½ years later.

SUMMARY OF EVIDENCE

Data now available from family-genetic, epidemiologic, and longitudinal studies clearly illustrate the high comorbidity between anxiety disorder and depression in children. The high-risk studies show:

1. Offspring of depressed parents are at high risk for depression and anxiety disorders; that is, their risk for developing these disorders is much higher than that known for children of nondepressed and nonanxious parents.
2. Offspring of parents with anxiety disorders are at high risk for anxiety disorders and depression.
3. The adult relatives of children with depression or with anxiety disorders have high rates of depression and of anxiety disorders.
4. The specificity of these disorders to depression and anxiety is unclear because a host of other disorders are also represented in high-risk offspring.
5. There is a high co-occurrence of depression and anxiety in children, although the chronology of these disorders is not clear.
6. Although there are no data yet available on longitudinal studies of children with anxiety and depressive disorders into adulthood, the shorter-term follow-up studies suggest the continuity and persistence of depression.

FUTURE RESEARCH

The findings presented here raise several research issues and point to future directions.

Diagnostic Hierarchies of DSM-III

The high-risk studies thus far have been based on DSM-III criteria. It is possible that the hierarchies of DSM-III could obscure the presence of an existing anxiety disorder in a proband parent because anxiety is not diagnosed in DSM-III if it occurs in the presence of major depression. While this hierarchy has been eliminated from DSM-III-R, the current published data are based on DSM-III. The use of hierarchies could be inadvertently exaggerating the findings on comorbidity because many of the probands may have anxiety disorders that are not diagnosed. In a study that did not use the conventional DSM-III hierarchy and diagnosed anxiety disorder even if it co-occurred with major depression, 87.5% of 56 probands with major depression had some anxiety disorder at some point in their lifetime (Weissman, Leckman, Merikangas, et al. 1984).

Concordance in Diagnosis Between Parents

Since assortative mating for psychiatric disorders is high, any study of children must take into account the diagnosis of the spouse. For example, in the study of 56 probands with major depression, 32.4% of their spouses had a major depression and 44.6% had an anxiety disorder at some point in their life (Weissman, Leckman, Merikangas, et al. 1984).

If a depressed and/or anxious proband is married to a spouse with depression and/or anxiety, then these factors could account for the high rates of depression and/or anxiety in the offspring studied. It is not possible to study these issues from the available data because the comorbid disorders in the proband and the diagnosis of the spouse are often not included in the published findings.

Studies of diagnostically pure proband groups (i.e., depressed patients with no other psychiatric disorders, current or in the past) who are married to a spouse who have similar disorders or who never have had a psychiatric illness are rare. We have such a study underway, but these patients are difficult to locate either in community or clinic samples. When we have attempted to examine the role of illness in offspring, taking into account comorbidity and diagnosis in both parents, we still found equal transmission of depression and anxiety in the offspring (Weissman, Leckman, Merikangas, et al. 1984).

The Specific Anxiety Disorders

Most of the studies look at anxiety disorders without differentiating between the specific types. Further study of the specific anxiety dis-

orders and their comorbidity with depression would be useful. For example, while major depression and anxiety disorders generally co-occur, it is unclear if this is true for all anxiety disorders.

Parent-Child Reports

The discrepancies between parent and child reports of a child's psychopathology should be considered in future analyses. There is considerable agreement that parents and children do not agree on the nature and extent of the children's diagnosis (Weissman, Wickramaratne, Warner, et al. 1987). Although many studies now use best-estimate diagnoses of children based on all available information, there is inconsistency in the published findings. Independent reports of data by parent and by child as well as by a child psychiatrist would be useful in comparing results.

Long-Term Follow-Up

As of this writing, there is not one published study of the continuity into adulthood of depression or anxiety disorders in children. Several studies are underway, and these will help clarify the diagnostic issues.

Familial Aggregation and Discrepancy With Adult Studies

The co-occurrence of depression and anxiety disorders in individuals has been found in studies of adults and of children. The transmission of anxiety and depression across the generations has been shown in samples of children and parents. However, not all family studies of adults have shown the familial aggregation of depression and anxiety disorders (see Crowe, Noyes, Pauls, et al. 1983; Harris, Noyes, Crowe, et al. 1983; Leckman, Weissman, Merikangas, et al. 1983, 1984).

The discrepancy between the adult and children's studies may be due to diagnostic comorbidity and the absence of proband groups with pure anxiety disorders, differences in diagnostic approaches, the small number of studies of anxiety disorders that have included children, and the tentative state of psychiatric diagnosis in children. The familial transmission of anxiety and depression across the ages is still unresolved.

CONCLUSION

The evidence from studies of children lends further support to the comorbidity of depression and anxiety disorders. However, the data

are not without problems. For example, studies of sampling from probands with anxiety disorders are small; all the specific anxiety disorders have not been studied; control groups are sometimes lacking; and family history rather than interviews are sometimes used. Most important, the stability of childhood disorders and their continuity to adulthood is unclear. From a research perspective, the importance of understanding affective and anxiety disorders in children should not be overlooked. The model in recent genetic studies has been Huntington's or Alzheimer's disease, both disorders of late onset. Inclusion of children in pedigree studies of these late-onset disorders would be uninformative or even misleading. The child would not have entered the age of risk for the disorder and could be incorrectly counted as unaffected. By contrast, affective or anxiety disorders have quite early onsets (Kashani 1982). Selection of a proband who is an adolescent makes it more likely that the family members will be alive and available for extended pedigree studies; for example, a 14-year-old child will likely have living siblings, parents, and grandparents. With the increasing availability of a genetic map, small nuclear families with at least three affected members will become a powerful tool for understanding linkage of markers for a chromosome to a disorder. If the child is a proband, there is more likelihood of finding sibling pairs and trios for study. The ability to diagnose children accurately will increase the odds of finding these families for study. The clarification of the overlap and distinction between disorders in children will be important in judging who is affected in pedigree studies.

Psychiatric studies of children also provide an opportunity for answering questions about the nature of disorders before the social and economic consequences of illness have occurred. Lastly, studies of first onset may provide information on the sequence of occurrence of disorders and on the factors associated with their onset and may clarify the problem of comorbidity.