chological Medicine, 1994, 24, 69–80.

Comorbidity and co-transmission of alcoholism, anxiety and depression

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NOPSIS This paper applies data from a family study of depression to assess patterns of morbidity and co-transmission of alcoholism, anxiety disorders, and major depression. We found hat all three disorders were strongly transmissible; however, alcoholism demonstrated the greatest egree of familial aggregation. The pairwise associations among depression, anxiety and alcoholism ndicated that the traits are co-transmitted in families, especially depression and anxiety. Individual ssociations between traits (or comorbidity) were entirely explained by transmitted (perhaps enetic) agents, because the correlations between traits due to random environment were not ignificant. These findings have important implications for treatment, psychiatric nosology, and etiological investigations of these conditions.

INTRODUCTION

'As no two faces, so no two cases are alike in all respects, and unfortunately it is not only the disease itself which is so varied but the subjects themselves have peculiarities which modify its action...' (Sir William Osler, 1895)

The term 'comorbidity' was introduced by Feinstein (1970) as an admonition to investigators of clinical trials to assess co-occurring disorders that may have impact on treatment outcome. In psychiatry, multiple diagnoses have been shown to occur frequently in both clinical and epidemiological surveys (Boyd *et al.* 1984; Regier *et al.* 1990). Numerous artefactual sources of co-occurrence must be excluded before conclusions regarding associations between disorders can be drawn. These include: sampling bias resulting from exclusive investigation of clinical samples, known as Berkson's bias (Berkson, 1946); failure to sample across relevant strata of the population, thereby yielding associations attributable to confounding factors; and overlapping diagnostic criteria elevating the prior probability of the co-occurrence of these conditions.

Relationship between depression and alcoholism: previous studies

The combination of alcoholism and major depression within individuals has been frequently observed in both treated and untreated samples. The results of community surveys demonstrate that alcoholism and major depression are associated in persons who have not been ascertained in clinical studies (Weissman & Meyers, 1980; Boyd *et al.* 1984; Helzer & Pryzbeck, 1988). However, there are few clinical differences between alcoholics with either primary or secondary depression. Indeed, Woodruff *et al.* (1979), reported that patients with alcoholism and depression resemble alcoholic patients without depression more than they resemble patients with depression only. Family studies of alcoholics (Cloninger *et al.* 1979) and of depressives (Merikangas *et al.* 1985) have demonstrated the independence of the familial transmission of these two conditions. Moreover, the results of an investigation of concordance for anxiety disorders and depression among alcoholic twins suggested that anxiety and depression are more likely to be a consequence than a cause of alcoholism (Mullan *et al.* 1986).

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In a recent review of the literature on comorbidity of depression and alcoholism, Merikangas & Gelernter (1990) concluded that although alcoholism and depression are transmitted independently in families, both major depression and bipolar depression are associated with alcoholism within individuals. However, the nature of the relationship between bipolar and non-bipolar depression and alcoholism differs in the following way: whereas major depression is often a consequence of alcoholism, bipolar depression is commonly antecedent to alcoholism.

Relationship between the anxiety disorders and depression: previous studies

The evidence regarding the relationship between the anxiety disorders and major depression has been extensively reviewed by several investigators (Breier *et al.* 1985; Stavrakaki & Vargo, 1985; Maser & Cloninger, 1990). Evidence for this relationship has been derived from several sources, including clinical studies of symptom patterns, treatment response, clinical course, family studies, and biological parameters among patients with these disorders, and, more recently, studies of the associations between these disorders in epidemiological surveys (Murphy *et al.* 1984; Regier *et al.* 1990).

Data on comorbidity of anxiety and affective disorders from family and twin studies were reviewed by Merikangas (1990). The results of numerous studies were inconsistent with respect to the familial overlap between anxiety and depression: there was evidence for pure forms of both major depression and anxiety disorders, with the 'pure' forms of anxiety breeding true within families (Cloninger *et al.* 1981; Van Valkenburg *et al.* 1984; Coryell *et al.* 1988) and also for a 'mixed' form of anxiety and depression, in which anxiety and depression in families appear to have shared underlying aetiological factors (Leckman *et al.* 1983; Kendler *et al.* 1986; Maier *et al.* 1988).

Relationship between alcoholism and anxiety: previous studies

Evidence for an association between alcoholism and anxiety has emerged from clinical studies of patients with alcoholism (Woodruff *et al.* 1972; Mullaney & Trippett, 1979; Bowen *et al.* 1984; Smail *et al.* 1984; Weiss & Rosenburg, 1985; Chambless *et al.* 1987) and patients with anx disorders (Lader, 1972; Marks & Lader, 19 The findings of epidemiological studies con the association between anxiety and alcohol as well (Helzer & Pryzbeck, 1988; Regier *e* 1990). Recent reviews of this association h been presented by Wesner (1990), Kushner *e* (1990), and Cowley (1992). Kushner *et al.* (19 concluded that the association between anxiety disorders and alcoholism could chie be attributed to the co-occurrence of the phob disorders and alcoholism, rather than to c morbidity with panic and generalized anxie states.

The family studies of probands with anxie disorders have also shown a significant increa in the risk of alcoholism among first-degr relatives (Cohen *et al.* 1951; Noyes *et al.* 197 Munjack & Moss, 1981; Harris *et al.* 1983 Indeed, Cohen *et al.* (1951) were so convinced o a familial association between alcoholism an 'neurocirculatory asthenia' that alcoholics i the families of the latter group were considere to be affected with the same disease. Howeve family studies of alcoholics have not system atically examined the prevalence of anxiety disorders among the relatives, nor have they studied patterns of transmission of the two disorders.

Use of familial transmission data to assess mechanisms for associations

The present study examines the nature of the associations between disorders using data from a family study to examine whether the disorders or combinations thereof co-segregate or 'breed true'. If there is a true association between two or more disorders, there are two general mechanisms by which the association may occur: disorders *A* and *B* could be causally associated, with *A* causing or predisposing to *B* or vice versa; or the two disorders could share a common aetiology, with *A* and *B* being alternative manifestations of the same underlying factor or factors, or different stages of the same disease.

If the relationship between two disorders were aetiological, with one condition causing the other, it would be expected that relatives would manifest an increased risk of the causal disorder and the combination of the two syndromes, but not the pure form of the other disorder. For example, if anxiety caused depression, relatives

probands with anxiety should have an eased rate of major depression, but only in presence of a lifetime history or concomitant ession of anxiety. Conversely, if depression ed anxiety, rates of anxiety would be ted among relatives of probands with ession, but only in combination with ression. An aetiological relationship between ression and anxiety could result from any of following situations: anxiety could cause r-responsivity of neuro-receptors which n neurotransmission leading to depression; ression could be a side effect of drug tment of anxiety; anxiety and depression ld be different expressions of the same disease oss the course of this condition (e.g. anxiety prominent in early phase and depression ominent in later stages); or depression could a psychological response to anxiety, with ronic anxiety causing the affected person to velop a negative self-image, impaired functoning and ultimately depression.

In contrast, if the two disorders were manistations of similar underlying factors, relatives probands with pure forms of either disorder ould have elevated rates of pure forms of the ther disorder as compared to expected popuation rates. Therefore, relatives of probands ith 'pure' depression should have an increased sk of 'pure' anxiety and the converse. Examples shared aetiological factors leading to deression and/or anxiety may be as follows: both esult from common biological environmental isk factors (e.g. birth control pills or other drugs, such as antihypertensives), viral infection or a nutritional factor; both could be effects of the same gene(s) (e.g. a gene involved in dopamine metabolism); both could result from common exposure to a prenatal environmental factor (e.g. maternal alcohol use); or both could result from a common non-biological environmental factor (e.g. a disruptive family environment associated with an alcoholic parent or parental abuse or neglect). In those cases, manifestation of the disorder could develop through distinct pathways by one of the following mechanisms: a genetic factor independent of that which leads to anxiety or depression; age at exposure to a particular risk factor; or a particular environmental factor such as lack of social support or a chronically stressful environment.

This paper applies data from a family study of depression to examine simultaneously the above-cited mechanisms for the associations between alcoholism, anxiety disorders, and major depression. These analyses build on previous work which employed data on familial aggregation to identify sources of heterogeneity of major depression. The data showed that the following factors were independently associated with the highest familial aggregation of affective disorders: early age of onset, anxiety disorders, and secondary alcoholism (Weissman *et al.* 1986).

METHOD

Probands

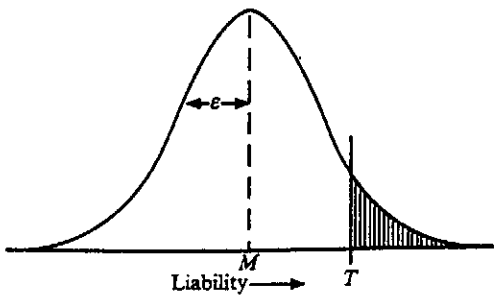
There was a total of 215 probands: 89 with non-hospitalized major depression, 44 with hospitalized major depression, and 82 normal community controls. The control group was drawn from a population sample and had no evidence of psychiatric disorders or treatment in an earlier epidemiological study conducted in 1967 and again at re-entry to the study in 1976. The depressed probands and controls were group-matched by sex and age (Weissman *et al.* 1982). The average social class level, which was 3 on the Hollingshead scale, did not differ between the depressed and normal probands (Hollingshead, 1957).

For this analysis, the depressed probands were classified into mutually exclusive categories according to the presence or absence of a lifetime history of alcoholism and anxiety disorders (i.e. depression only, depression and alcoholism, depression and anxiety, or depression with both anxiety and alcoholism). Probands with antisocial personality or primary alcoholism based on age at onset of alcoholism preceding that of major depression or an anxiety disorder, either according to direct interview or by family history, were excluded from the study. The number of probands and relatives according to this classification is presented in Table 1.

The lack of proband groups with 'pure' anxiety or alcoholism does not preclude our ability to test the models because the analysis is done conditional upon the probands rather than employing the frequency of comorbidity in probands. The high frequency of disorders without major depression in the relatives enables

Table 1. *Numbers of probands with Alcoholism, Anxiety and/or Depression*

Proband groups	Probands (*N*)	Relatives (*N*)
Alcoholism + Anxiety + Depression	13	76
Alcoholism + Depression	6	42
Anxiety + Depression	67	419
Depression only	47	273
Normal	82	521
Total *N*	215	1331



$M = 0$
$\varepsilon = 1$

FIG. 1. Polygenic thresholds model of disease transmission. (■, Affected.)

us to test the cross-transmission of these conditions.

Diagnoses in relatives

Lifetime diagnostic estimates using modified RDC criteria were made on a total of 1331 living and deceased first-degree relatives of the probands. Sources of information used in making diagnoses included direct interviews, with 60% of the living relatives, medical records, and family history information, which was obtained systematically from multiple informants. Because the adequacy of information regarding the relatives varied, diagnoses were made according to the degree of certainty (i.e. possible, probable, definite). For the analysis reported herein, only probable or definite diagnoses were included. All diagnoses were made blindly with respect to the status of the proband. A more detailed description of the design and methods of this study is presented by Weissman *et al.* (198 Gershon *et al.* (1982).

The diagnoses in relatives in the pr analyses were not mutually exclusive an cluded the following disorders: major pression, which differed from the RD requiring a four-week duration and eviden social role impairment; anxiety disorder, w included agoraphobia, simple and social pho panic disorder, and generalized anxiety disor all of which were specified by modified DSM symptomatic criteria with evidence of social impairment, and which could have occur solely during episodes of depression and coholism, which included probable or defi RDC alcoholism.

Statistical analysis

Proportional hazards analyses

The proportional hazards (PH) model, a gener quasi-parametric model introduced by C (1972), was used to analyse the data. The P model applies the multiple regression method a survival distribution, or another one-tim event such as onset of a disorder. The P procedure yields the regression coefficient β (an its standard error) of an independent variable i predicting the age-specific incidence of th outcome variable (i.e. diagnosis of relatives while simultaneously controlling for other in dependent variables which may be related to th outcome (Lee, 1980). A hazard function is the probability that a person becomes affected by age $t+1$, given that he is unaffected at age t. In this analysis all main effects and two way interactions were entered into the model in a stepwise fashion, in order of statistical sig nificance.

In the present study, three separate analyses were employed to examine the age-specific incidence of major depression, anxiety disorder and alcoholism in the relatives according to the proband diagnostic groups. Previous analyses of these family study data revealed that the diagnoses of relatives were significantly associated with sex, year of birth, and interview status, but not with sex of the proband or the generation of the relative. Therefore, the effects of sex, year of birth and interview status of the relatives, were initially included in each model. The statistical significance of the independent variables was determined by likelihood ratio χ^2

ble 2. *Parameters of polygenic-multifactorial shold model for co-transmission of pression, Alcoholism and Anxiety*

T_d	Threshold for Depression
T_{al}	Threshold for Alcoholism
T_{an}	Threshold for Anxiety
	onents of variance
H_d	Transmissibility of Depression
H_{al}	Transmissibility of Alcoholism
H_{an}	Transmissibility of Anxiety
ρ_{d-al}	Correlations between transmissibility for Depression and Alcoholism
ρ_{d-an}	Correlations between transmissibility for Depression and Anxiety
ρ_{al-an}	Correlations between transmissibility for Alcoholism and Anxiety
τ_{d-al}	Correlations between environmental components for Depression and Alcoholism
τ_{d-an}	Correlations between environmental components for Depression and Anxiety
τ_{al-an}	Correlations between environmental components for Alcoholism and Anxiety

tatistics which compare the relative fit of the models with and without the independent variable, in the presence of covariates (Cox, 1972). The computer program used in the analysis was the PHGLM procedure of the Statistical Analysis System (Reinhardt, 1980). The anti-logarithm of the β and its confidence limits yields a risk ratio and its confidence limits, which are interpreted as relative risks.

Co-transmission analysis

The model that we used to study the co-transmission of the three disorders was a trivariate multifactorial threshold model, with one dimension for each disorder. This is a generalization of the univariate general multifactorial model of disease transmission originally proposed by Falconer (1965). The univariate liability (for each disorder), or propensity for transmitting the disorder, is plotted on the x-axis in Fig. 1. The shaded section represents the proportion of affected individuals. The multifactorial model specifies that numerous genetic and environmental factors are involved in an individual's liability for a particular disorder. The liability is assumed to be normally distributed with a mean of 0 and a variance of 1. The threshold T is defined as the point after which the disorder becomes manifest. The location of T is determined by the population prevalence of the disorder (i.e. the area under the normal curve beyond T).

This model was extended to a trivariate multifactorial model to determine whether associations among the three traits could be attributed to familial (transmitted) or non-familial (non-transmitted) factors. We have previously employed a bivariate version of this model to investigate the co-segregation of depression and migraine (Merikangas *et al.* 1988). The analysis is based on frequencies of both traits among the relatives of probands with different diagnoses (e.g. none or both traits). Reich *et al.* (1979) further extended the bivariate method to nuclear families as the unit of analysis, which provides additional power, but induces considerably greater computational complexity. A bivariate version of the model employed here was described by Smith (1976). Here we assume three distinct continuous liabilities underlying depression, alcoholism and anxiety. The liabilities are assumed to have a trivariate normal distribution, whose correlation matrix is determined by both transmitted and non-transmitted components, as described below.

The following parameters of the model are given in Table 2: three threshold values T_d, T_{al}, and T_{an} for depression, alcoholism and anxiety, respectively; the three transmissibilities H_d, H_{al} and H_{an} for depression, alcoholism and anxiety, respectively; the three pairwise correlations (ρ) between the transmissible components; and the three pairwise correlations (τ) between the environmental (i.e. non-transmitted) components for the three traits, respectively. Hence, there is a total of 12 independent parameters, plus the three random environmental components $E_d(=1-H_d)$, $E_{al}(=1-H_{al})$ and E_{an} $(=1-H_{an})$ respectively. The derivations of the correlations in liabilities for probands and relatives are presented in the Appendix.

The units of analysis are the frequencies of the eight possible outcomes among the relatives of the five different types of probands, yielding a total of 40 cells, 35 of which are independent (see Table 5). The formulas for determining these rates in terms of the model parameters have been given by Smith (1976). In the best model the three environmental correlations (τ) were set to zero, leaving 9 parameters (see Table 6). Because there are 35 independent cells and 9

Table 3. *Diagnoses in probands and relatives*

Diagnosis of proband	Diagnoses in relatives (%)*			
	Alcoholism	Anxiety disorder	Major depression	Total (*N*)
Alcoholism + Anxiety + Depression	32·9	25·0	25·0	76
Alcoholism + Depression	23·8	9·5	21·4	42
Anxiety + Depression	15·0	12·9	17·0	419
Depression only	7·0	9·9	8·1	273
Normal	9·0	5·4	5·6	521
Total				1331

* Non-mutually exclusive.
† Mutually exclusive

Table 4. *Results of proportional hazard analyses of comorbidity in probands on disorders in relatives* ($N = 1331$)

	Disorders in relatives (adjusted risk ratio (±95% confidence limits))		
	Major depression	Anxiety	Alcoholism
Disorders in proband			
Depression *v.* Not	1·5 (0·9–2·6)	2·2 (1·3–3·4)**	1·3 (0·8–2·2)
Anxiety *v.* Not	1·7 (1·1–2·6)**	1·2 (0·8–2·0)	1·7 (1·1–2·6)*
Alcoholism *v.* Not	1·5 (1·0–2·4)	1·3 (0·7–2·2)	2·5 (1·7–3·8)***
Disorders in relatives			
Depression *v.* Not	Not applicable	3·0 (2·1–4·4)***	2·2 (1·5–6·0)***
Anxiety *v.* Not	3·2 (2·1–1·7)***	Not applicable	1·1 (0·6–1·7)
Alcoholism *v.* Not	2·6 (1·8–3·9)***	1·0 (0·6–1·7)	Not applicable
Covariates for relatives			
Interviewed *v.* Not	1·1 (0·8–1·5)	5·7 (4·5–8·8)***	1·8 (1·27–2·56)***
Female *v.* Male	2·0 (1·4–2·9)***	1·6 (1·1–2·4)*	0·3 (0·2–0·4)***
Year of birth	0·0052 (0·004)***	0·0057 (0·005)***	0·0051 (0·004)***

* = $P < 0·05$; ** = $P < 0·01$; *** = $P < 0·001$.

model parameters (in the best reduced model), it is possible to perform an overall goodness-of-fit test of the model. Here we perform a likelihood ratio χ^2 goodness-of-fit test with 26 degrees of freedom. To test hypotheses about significance of various parameters, we perform likelihood ratio tests, which have an asymptotic χ^2 distribution with one degree of freedom for each variance component set equal to zero.

Likelihoods for this model were obtained from the Fortran computer program COSEG (Risch N, an unpublished FORTRAN program for multivariate polygenic threshold analysis). Likelihoods were maximized under the program MAXLIK (Kaplan & Elston, 1972).

RESULTS

The 215 probands were classified in a mutually exclusive manner according to the presence of comorbid disorders including alcoholism, anxiety, and depression, alcoholism and depression, anxiety and depression, depression only and normal (i.e. no psychiatric diagnosis). Anxiety disorders are comprised of panic disorder, generalized anxiety disorder and/or phobic disorder. Rates/100 of non-mutually exclusive diagnoses among the relatives of each of the proband groups are shown in Table 3.

These results show that rates of alcoholism were increased among the relatives of probands

Table 5. *Observed and model-predicted numbers of disorders in relatives by proband disorders*

Proband disorders	Disorders in relatives (*N* observed (predicted))								
	DEP+ALC+ANX	DEP+ALC	DEP+ANX	ALC+ANX	DEP only	ALC only	ANX only	Other/no diagnoses	*N* at risk
DEP+ALC+ANX	8 (2·3)	1 (3·7)	4 (2·7)	2 (2·4)	6 (5·9)	14 (13·3)	5 (4·9)	36 (40·7)	76
DEP+ALC	1 (0·8)	3 (1·7)	1 (1·0)	0 (1·1)	4 (2·6)	6 (8·1)	2 (2·1)	25 (24·6)	42
DEP+ANX	4 (6·2)	12 (9·9)	13 (17·1)	8 (6·7)	42 (36·8)	39 (34·7)	29 (32·8)	272 (274·8)	419
DEP only	0 (2·4)	1 (4·8)	8 (6·8)	0 (3·2)	13 (18·5)	18 (22·6)	19 (16·1)	214 (198·3)	273
Normal	4 (1·3)	7 (3·8)	5 (4·3)	1 (2·3)	13 (18·3)	35 (32·1)	18 (15·4)	438 (443·5)	521

DEP = Depression; ALC = Alcoholism; ANX = Anxiety.

with alcoholism, but also to a lesser extent among those probands with anxiety and depression as compared to normal controls or those with depression only. Anxiety disorders, on the other hand, were elevated among the relatives of all of the depressed probands as compared to the normal controls, with a significantly elevated risk among relatives of the probands with all three disorders. Rates of major depression were found to be increased among the relatives of the depressed probands with comorbid disorders, but only slightly among those probands with depression alone as compared to normal controls.

The results of the application of the Cox proportional hazards model are shown in Table 4. The major purpose of this analysis was to investigate the transmission and cross-transmission of major depression, anxiety disorders, and alcoholism between probands and relatives while controlling simultaneously for comorbidity in the relatives. Because of the strong effects of interview status (with only 40% of the relatives having been interviewed directly), year of birth and sex, these factors were included in all analyses.

In the upper third of the Table, it is shown that after controlling for the latter factors, depression in the proband was associated with anxiety disorders, but only slightly with depression or alcoholism, in the relatives; anxiety in the proband was associated with major depression and alcoholism in relatives, but only slightly with anxiety disorders in the relatives; and alcoholism in the proband was strongly associated with alcoholism in the relative.

In the middle third of the Table, the associations between major depression, anxiety and alcoholism within the relatives (i.e. comorbidity) with the other two disorders are shown. The results indicate that depression in the relatives was significantly associated with both anxiety disorders and alcoholism; anxiety disorders were significantly associated only with depression; and alcoholism was associated only with depression.

These results show a strong degree of cross-transmission of both anxiety and depression in probands and their relatives, because comorbid anxiety in probands was associated with an increased risk of depression in relatives and the converse. Whereas depression and anxiety in probands was associated with a mildly elevated risk of alcoholism in relatives, alcoholism in probands was more strongly associated with increased familial aggregation of alcoholism. This suggests that a familial association between depression and alcoholism may be partly attributable to shared liability between anxiety disorders and depression.

Because the relatives also exhibited a high frequency of comorbidity for these disorders, the relatives were then classified into mutually exclusive diagnostic categories (Table 5). This mutually exclusive cross-classification served as the data for the co-transmission analysis presented.

Despite the lack of probands with 'pure' alcoholism or 'pure' anxiety disorders, symmetry should exist between the risk of anxiety disorders in relatives of probands with alcoholism, and the risk of alcoholism in the relatives of probands with anxiety disorders, if the base rates of these two conditions approximate those in the general population. We have compared the age-specific rates of major depression, anxiety disorders, and alcoholism among the relatives of controls to the lifetime rates reported in the Epidemiologic Catchment Area (E.C.A.) (Boyd *et al.* 1984; Helzer & Pryzbeck, 1988;

Table 6. *Parameters (standard errors) of multifactorial threshold models for co-transmission of Depression, Alcoholism and Anxiety*

	Full model	Best-fitting model
T^a	1·586 (0.084)	1·616 (0·074)
T_{al}	1·396 (0·073)	1·435 (0·059)
T_{an}	1·676 (0·079)	1·698 (0·068)
H_d	0·434 (0·098)	0·456 (0·089)
H_{al}	0·925 (0·201)	0·889 (0·191)
H_{an}	0·457 (0·110)	0·474 (0·100)
$\rho_{d\text{-}al}$	0·316 (0·174)	0·427 (0·108)
$\rho_{d\text{-}an}$	1·000	0·992
$\rho_{al\text{-}an}$	0·316 (0·108)	0·316 (0·104)
$\tau_{d\text{-}al}$	0·463 (0·993)	0*
$\tau_{d\text{-}an}$	0·078 (0·116)	0*
$\tau_{al\text{-}an}$	0·000	0*
-lnL†	1306·84	1307·58

* Constrained in this model.
† Negative logarithm of likelihood.

Regier *et al.* 1990) study. We found that they closely approximate population base rates (major depression, 5·7; panic disorder, 1·4; and alcoholism 8·5). Additionally, the high rates of disorders without major depression in the relatives yields sufficient power to enable us to test the cross-transmission of these conditions.

Table 6 presents the results of the analysis of the co-transmission of alcoholism, anxiety, and depression between the depressed and normal probands and their relatives. Transmissibility estimates (i.e. that incorporate both genetic and environmental transmissibility) derived from this model were 0·89 for alcoholism, 0·47 for anxiety, and 0·46 for depression.

The correlations in transmissibility for anxiety and depression, anxiety and alcoholism, and depression and alcoholism, were also highly significant. There was complete correlation of the transmissibilities for anxiety and depression. In contrast, none of the effects of the environmental correlations was significant. The results can be summarized as follows.

(1) There was strong independent transmission of alcoholism alone;

(2) there was no unique transmission of either depression or anxiety, for nearly all of the transmissibility between the two disorders was shared;

(3) there was significant but incomplete sharing of transmissibility between alcoho and anxiety, and between alcoholism and pression;

(4) the effects of shared random envir mental components, were insignificant; and

(5) more than half of the variance in liabi for both depression and anxiety could not attributed to shared family factors (either gen or environmental) suggesting that unique e vironmental factors play a major role in t expression of these conditions.

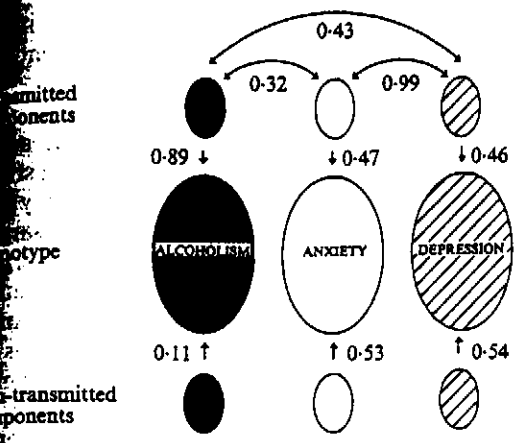
These results are summarized schematically Figure 2.

The likelihood ratio goodness-of-fit test f the best model (given in Table 6) was highl significant (i.e. $\chi^2 = 48{\cdot}62$, 26 df, $P < 0{\cdot}005$ The expected numbers of relatives with vario diagnoses predicted by this model are given Table 5. Nearly half (23·0) of this χ^2 comes fro the observations in column 1 (relatives with a three disorders). In particular, among the rela tives of probands with all three disorders, ther were 8 relatives with all three disorders, where only 2·3 were expected ($\chi^2 = 14{\cdot}1$). It turned ou that 6 of the 8 observed individuals in thi category came from the same family. Aside from this family, the model gives an acceptable fit to the data. This exceptional family with 7 individuals with all three diagnoses (proband+6 relatives) appears to be an outlier, and may represent a unique event.

In order to investigate whether the results of these models applied to specific anxiety disorders, we also applied this model to the co-segregation of panic disorder (rather than all anxiety syndromes), alcoholism, and major depression. In addition, we also repeated the analyses for the subset of relatives who were interviewed directly. In both of these analyses the variance components and correlation estimates were similar to those for the original analysis.

DISCUSSION

The findings described herein appear to be generally consistent with those in the literature regarding the familial transmission and associations between these disorders, taken two at a time. Although strong associations between depression and anxiety disorders, and between



2. Co-transmission of alcoholism, anxiety and depression. gle-headed arrows represent variance components; double- ded arrows represent correlation.)

lcoholism and the anxiety disorders within individuals have been described by numerous investigators, the simultaneous co-transmission of all three disorders has not been investigated previously. All three disorders were strongly transmissible; but alcoholism demonstrated the greatest degree of familial aggregation. This was particularly surprising in light of the exclusion of probands with primary alcoholism from the study. The majority of the variance in the transmission of alcoholism was unique to alcoholism, as previously shown by Angst (1966) and Cloninger *et al.* (1979).

In this analysis, we have investigated the associations among depression, anxiety, and alcoholism. Both the hazards analyses and cosegregation analyses demonstrated that these traits are co-transmitted in families, especially depression and anxiety. The co-transmission analysis also revealed that the observed-within-individual associations between traits (or comorbidity) could be explained entirely by transmitted (perhaps genetic) agents, as the correlations (τ) between traits due to random environment were not significant.

The lack of significance of the correlations in the environmental components in the threshold models does not imply that environmental factors do not contribute to the expression of the conditions considered in this work. However, the results of the present study suggest that random environment does not have a major role in the comorbidity of these conditions. Rather, the environmental contributions to the aetiology of these disorders are unique to each of the three conditions.

These findings show that the comorbidity and co-transmission of these disorders are not an artefact of treatment-seeking bias, because the analyses were based on information about relatives of treated probands who were not themselves ascertained from treatment settings and relatives of normal controls selected at random from the general population. Furthermore, the results of epidemiological surveys demonstrate the associations in persons randomly selected from the community. Data presented by Regier *et al.* (1990) from the ECA study revealed strong associations between alcohol abuse or dependence with phobic disorders (odds ratio = 2·4), panic disorder (odds ratio = 4·3) and anxiety disorder (odds ratio = 1·5). Consistent with the findings of the present study, depression and anxiety disorders were even more strongly associated than was alcoholism with either disorder, with the odds ratios exceeding 15 for both phobia and panic with depression.

Based on the observation that persons with anxiety disorder tend to self-medicate with alcohol, numerous studies of clinical samples do suggest that anxiety disorders may be aetiologically associated with alcoholism. Lader (1972) observed that most anti-anxiety drugs are self-administered, with alcohol being the most common agent. Smail *et al.* (1984) and Stockwell *et al.* (1984), in discussing the possible mechanisms for this association, noted that most patients with anxiety reported that they had deliberately used alcohol in order to cope in feared situations. The likelihood of alcoholism being secondary to anxiety is also suggested by the finding that persons with both disorders tend to exhibit the anxiety prior to the onset of alcoholism, often by several years (Lader, 1972; Cadoret *et al.* 1985). Clinical data from the present study are compatible with this self-medication hypothesis, because the onset of the anxiety disorders preceded that of alcoholism in nearly 65 % of those persons with both disorders.

Results of other studies suggest that alcoholism may lead to the manifestation of anxiety as well (Mullan *et al.* 1986). Because anxiety is also a common symptom of alcohol withdrawal,

there is now a consistent body of experimental work indicating that prolonged alcohol consumption leads to marked deterioration of affect, characterized by anxiety and depression (Cadoret *et al.* 1985).

Evidence from the multifactorial threshold models contradict this aetiological association, because alcoholism was not more likely to co-occur in conjunction with anxiety disorders than it was to occur alone among the relatives of probands with either anxiety or alcoholism. Moreover, the results of the hazard analyses showed that anxiety in the proband was a risk factor for alcoholism in the relative, controlling for the relative's anxiety. However, it is possible that the retrospective assessment of lifetime diagnosis in this study led to an underestimation of the prevalence of anxiety disorders among both probands and relatives with alcoholism.

The third possible explanation for associations between disorders (described above), that the conditions are manifestations of common underlying factors that result in the expression of either disorder or both, was supported by our data. Alcoholism and anxiety disorders were found to share some underlying transmissible factors. To our knowledge, this finding has not been previously reported, nor have there been systematic studies that have examined possible mechanisms for the transmissible association between the two disorders.

The strong association in the transmission of anxiety and depression suggests that these two disorders are also manifestations of shared underlying aetiological factors. These results confirm those of a cross-sectional twin study by Kendler *et al.* (1986) who reported shared genetic liability in the symptoms of anxiety and depression. Evidence regarding the similarity in neurochemical disturbances, response to the same pharmacological agents, and social and demographic risk factors also suggests shared aetiology. Furthermore, the overlap in clinical manifestations and course, with the majority of persons with non-bipolar depression expressing symptoms of anxiety both during and between acute episodes and vice versa, would suggest that there are similar aetiological factors involved in both anxiety and depression. Because all of our probands had non-bipolar depression, further studies involving probands with bipolar disorder and pure anxiety disorders without depression are necessary to complement the findings presented here.

These results require confirmation and validation in other samples with different ascertainment schemes than that of the present study. Samples of patients with alcoholism only and patients with anxiety disorders are necessary to examine whether the associations described above extend to probands with no lifetime history of major depression. Previous family studies suggest that there may be forms of anxiety disorders that do not share aetiological factors with major depression (Cloninger *et al.* 1981; Maier *et al.* 1988). We are currently completing a family study of probands with pure alcoholism and pure anxiety to examine whether these findings extend to these groups as well. Furthermore, the retrospectively-derived estimates of the ages of onset of these disorders are subject to unknown bias.

This paper illustrates the application of family studies to investigate possible mechanisms of association between disorders and for identifying homogenous subtypes of major psychiatric disorders. If non-bipolar 'pure' major depression, as defined according to current standardized criteria, is neither strongly transmissible in families nor found to have strong genetic components in its variation, as recently suggested by the adoption study of Cadoret *et al.* (1985) and the twin study of Torgersen (1985), future studies should determine to what degree it is a unique, valid category. The results of this study suggest that the traditional concept of depressive neurosis, with the prominence of features of anxiety and depression alternating across the lifetime course, may constitute a more valid diagnostic entity. Further longitudinal prospective studies and twin studies will be necessary to elucidate possible mechanisms for the associations between these disorders.

This research was supported in part by US National Institute of Health grants AA07080, DA05348, MH36197, a Research Scientist Development Award K02-MH00499 (Dr Merikangas) and HG 00348 (Dr Risch); and by the John D. and Catherine T. MacArthur Foundation, Mental Health Network I on the Psychobiology of Depression and Other Affective Disorders. The data derive from grant

MH28274 (Dr Weissman). The suggestions of Theodore Reich and Dr Susan E. Hodge are gratefully acknowledged.

APPENDIX
CORRELATIONS IN LIABILITIES FOR PROBANDS AND RELATIVES

Proband liabilities	Relative liabilities
X_1 = depression	X_2 = depression
Y_1 = alcoholism	Y_2 = alcoholism
Z_1 = anxiety	Z_2 = anxiety

$$\text{Corr}(X_1, Y_1) = \text{Corr}(X_2, Y_2) = H_d^{\frac{1}{2}} H_{al}^{\frac{1}{2}} \rho_{d\text{-}al} + E_d^{\frac{1}{2}} E_{al}^{\frac{1}{2}} \tau_{d\text{-}al}$$
$$\text{Corr}(X_1, Z_1) = \text{Corr}(X_2, Z_2) = H_d^{\frac{1}{2}} H_{an}^{\frac{1}{2}} \rho_{d\text{-}an} + E_d^{\frac{1}{2}} E_{an}^{\frac{1}{2}} \tau_{d\text{-}an}$$
$$\text{Corr}(Y_1, Z_1) = \text{Corr}(Y_2, Z_2) = H_{al}^{\frac{1}{2}} \rho_{d\text{-}an} + E_{al}^{\frac{1}{2}} E_{an}^{\frac{1}{2}} \tau_{d\text{-}an}$$
$$\text{Corr}(X_1, X_2) = \tfrac{1}{2} H_d$$
$$\text{Corr}(Y_1, Y_2) = \tfrac{1}{2} H_{al}$$
$$\text{Corr}(Z_1, Z_2) = \tfrac{1}{2} H_{an}$$
$$\text{Corr}(X_1, Y_2) = \text{Corr}(X_2, Y_1) = \tfrac{1}{2} H_d^{\frac{1}{2}} H_{al}^{\frac{1}{2}} \rho_{d\text{-}al}$$
$$\text{Corr}(X_1, Z_2) = \text{Corr}(X_2, Z_1) = \tfrac{1}{2} H_d^{\frac{1}{2}} H_{an}^{\frac{1}{2}} \rho_{d\text{-}an}$$
$$\text{Corr}(Y_1, Z_2) = \text{Corr}(Y_2, Z_1) = \tfrac{1}{2} H_{al}^{\frac{1}{2}} H_{an}^{\frac{1}{2}} \rho_{al\text{-}an}$$

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