

Sex-Specific Genetic Influences on the Comorbidity of Alcoholism and Major Depression in a Population-Based Sample of US Twins

Carol A. Prescott, PhD; Steven H. Aggen, PhD; Kenneth S. Kendler, MD

Background: Alcoholism and depression frequently co-occur, but the origins of this comorbidity remain uncertain. Most previous family, twin, and adoption studies of these disorders have used cases ascertained through treatment settings, who may differ from cases in epidemiological samples. We studied the importance of genetic influences on risk for lifetime comorbidity of major depression and alcoholism by means of a population-based twin sample.

Methods: Lifetime major depression (MD), alcohol abuse, and alcohol dependence were assessed by structured interview for both members of 3755 twin pairs from the Mid-Atlantic Twin Registry. Pair resemblance was analyzed by means of structural equation models.

Results: Individuals with MD were at significantly increased risk for alcohol dependence and for a combined diagnosis of alcohol abuse and/or dependence. History of MD in a twin significantly increased the risk of cotwin

alcohol dependence and alcohol abuse and/or dependence among identical male pairs and for alcohol abuse and/or dependence in identical female pairs, but not among male or female fraternal pairs. Results of structural modeling indicate that comorbidity occurs because the genetic and specific environmental sources of liability to MD overlap with those underlying alcohol dependence and alcohol abuse and/or dependence. This overlap was significant only within sex, not across sexes.

Conclusions: In this population-based twin sample, the familial transmission of MD and alcohol dependence was largely disorder specific. Comorbidity appears to be due to sex-specific genetic and environmental risk factors. The factors underlying depression in women do not appear to arise from the same factors underlying alcoholism in men.

Arch Gen Psychiatry. 2000;57:803-811

ALCOHOLISM and depression co-occur at levels higher than chance in clinical¹ and epidemiological²⁻⁴ settings. The cause of comorbidity is of substantial theoretical and clinical relevance because it complicates treatment and may alter prognosis.⁵

The most common approach to studying the causes of comorbidity has been with family studies.^{1,6} Methodological variation in definition of probands, use of family interview vs family history data, and the method used to define primary vs secondary diagnoses precludes simple summaries of the results. However, studies that began with alcoholic probands generally have found that relatives are not at increased risk for depression unless the proband also has depression.^{1,7-9} These findings are consistent with a phenotypic association between the two disorders, wherein the presence of alcoholism increases risk for

depression, but the vulnerability for the two disorders is transmitted independently within families.

Family studies based on probands with primary depression have yielded mixed findings. Some have found no increase in alcoholism among relatives unless the probands were also alcoholic.¹⁰⁻¹² Others have found increased alcoholism,¹³⁻¹⁵ but sometimes only among the relatives of female probands.¹⁶ The latter results have been used as evidence for a depressive spectrum in which women with depression plus alcoholism are viewed as having a more severe form and their relatives are at increased risk for depression and alcoholism compared with relatives of women with depression only.¹⁶

Studies beginning with treated alcoholics have found that the relatives of probands with both major depression (MD) and alcoholism were not at increased risk for alcoholism compared with relatives of probands with alcoholism alone.¹⁷⁻²¹ How-

From the Virginia Institute for Psychiatric and Behavioral Genetics, Department of Psychiatry, Medical College of Virginia of Virginia Commonwealth University, Richmond.

SUBJECTS AND METHODS

SUBJECTS

Subjects were from 2 longitudinal twin studies of psychiatric and substance-related disorders: one of female-female pairs (FF) and another of male-male and male-female pairs (MM/MF). Subjects were ascertained from the Virginia Twin Registry (now part of the Mid-Atlantic Twin Registry), which was formed by matching birth certificates to state records. Twins were eligible for participation if one or both were successfully matched and were born between 1934 (FF) or 1940 (MM/MF) and 1974. Inclusion in the FF study also required that both twins return a mailed questionnaire. Studies were limited to whites because participation levels by ethnic minority pairs were too low to permit valid estimates of genetic effects. Both studies were approved by our institutional review board. Subjects provided verbal consent for telephone interviews and written consent for in-person interviews and DNA collection.

The FF study included 2164 women interviewed in 1988 to 1989 and 276 ascertained subsequently. Data for the current study come from the fourth FF interview, which was conducted by telephone on 1945 (79.7%) of these 2440 women. Data from the MM/MF study come from the first interview, conducted in 1993 to 1996 by telephone with 6847 subjects (5120 male, 1727 female). Subjects were 18 to 56 years old (mean, 35.1 years; SD, 9.2 years) when interviewed and had a mean education of 13.4 years (SD, 2.6 years). Subjects from the two studies did not differ in educational level, but the FF sample was on average slightly older. Further details of sample ascertainment and characteristics are presented elsewhere.³⁶⁻³⁸

The individual-level analyses in this report are based on 8733 subjects (5081 male, 3652 female). Excluded are 59 subjects with incomplete diagnostic information. Twin-pair analyses are based on 7460 subjects (4421 male, 3039 female) from complete pairs with known zygosity and diagnostic data. Excluded are 1273 subjects whose cotwins were not interviewed or had incomplete data.

Same-sex pairs were classified as identical (monozygotic [MZ]) or fraternal (dizygotic [DZ]) on the basis of a discriminant function of questionnaire responses (about physical similarity and blood type) developed in the FF sample³⁹ and validated in the male sample by polymorphic markers (mean, 11.5 [SD, 11.9] markers per pair). Using this discriminant function, we could confidently assign zygosity to more than 93% of MM pairs. The remainder were assigned by genotyping (n=65) or review of photographs, audiotapes, and interview responses (n=32).

The complete pairs include 862 MZ male, 506 MZ female, 649 DZ male, 330 DZ female, and 1408 opposite-sex pairs. (This number includes 33 pairs created by all possible within-set pairings of members of 14 triplet sets and

1 quadruplet set. Exclusion of these pairs produced no appreciable change in the estimates, so we include them for completeness.)

MEASURES

Diagnostic criteria were adapted from standard structured interviews^{40,41} to permit evaluation of both *DSM-III-R*⁴² and *DSM-IV*⁴³ diagnoses. Interviewers had a master's degree in a mental health field or a bachelor's degree plus 2 years of relevant clinical experience and received extensive training. Members of a twin pair were interviewed by different interviewers who were blind to cotwin diagnosis.

Interrater reliability among 53 randomly selected FF subjects was $\kappa=1.0$ (± 0.05) for *DSM-III-R* AD⁴⁴ and $\kappa=0.96$ (± 0.04) for *DSM-III-R* MD.³⁹ The validity of our alcohol diagnoses is supported by their association with alcoholism treatment, alcohol consumption, and early drinking onset.⁴⁵⁻⁴⁷

Previous analyses of this sample⁴⁶ suggest little difference in twin resemblance for AD vs the broader AAD. However, previous research has found higher comorbidity for MD with AD than with AAD,¹ so we investigated both definitions. We selected *DSM-III-R* definitions because they are slightly broader than those based on *DSM-IV*, yielding greater comorbidity.

We also created a classification of nonsecondary AD, which includes only individuals whose alcohol-related episodes did not all occur entirely within an MD episode. This was assessed by an interview item or (for 71 subjects missing this item because it was omitted from an early version of the MM/MF interview) by review of interview protocols and audiotapes. Seventeen subjects were excluded because of missing data.

TWIN MODELS

We used a standard liability-threshold model to estimate the genetic and environmental contributions to twin-pair resemblance for their liability to depression and alcoholism. Liability is an inferred trait, assumed to be continuous and normally distributed in the population, with individuals who exceed a theoretical threshold expressing the disorder.⁴⁸ Individual differences in liability arise from 3 sources: additive genetic (G), genes whose allelic effects combine additively; common environment (C), all prenatal and postnatal environments shared by members of a twin pair; and specific environment (E), all remaining factors not shared within a twin pair, including measurement error (**Figure 1**). Comparing the resemblance of MZ and DZ twin pairs permits estimates of each source's contribution to individual differences in liability to a disorder, or to the covariance between disorders. (It is possible to include nonadditive genetic effects in twin models, but these have not been implicated in our univariate analyses of MD

ever, all the probands had severe alcoholism, so there may be a selection effect.

One limitation of this literature is that cases identified through treatment settings are likely to be more severe, have greater comorbidity, and may have different causes than epidemiologically ascertained cases.²² Two studies based on US epidemiological samples suggest that depression and alcoholism are not etiologically separ-

rate. Grant et al²³ and Dawson and Grant²⁴ found increased alcoholism in the relatives of probands with MD and found individuals with comorbid alcohol dependence (AD) plus MD reported higher prevalences of alcoholism among their relatives than individuals with AD only. Kendler et al²⁵ found significantly increased risk for MD among relatives of probands with alcohol abuse and/or dependence (AAD) and vice versa, although these asso-

and AD,^{37,46} so we do not consider them further.) There are G, C, and E sources for each diagnosis, and comorbidity can arise through a variety of mechanisms operating at the component or phenotypic level (**Figure 2**). These models make different predictions about the magnitudes of the cross-twin alcoholism-depression correlations in the different twin-pair types, so they will differ in how well they explain the observed data. Previous univariate results in these samples indicated significant sex differences in the genetic sources underlying MD³⁷ and alcohol disorders,⁴⁶ so we included these parameters in all models.

Our models assume random mating, equality of environmental effects for MZ and DZ twins, and no systematic biases associated with age, attrition, or pair completion. On the basis of several studies of AD and MD in spouses,⁴⁹⁻⁵² a large impact of nonrandom mating seems unlikely. Among same-sex pairs in our sample, similarity for lifetime MD and AD was not associated with the twins' similarity of childhood environment or frequency of adult social contact, supporting the validity of the assumption of equal MZ-DZ environments.^{37,46}

A previous report⁴⁶ from our group showed that women younger than 35 years had significantly higher prevalences of AD, but pair correlations did not differ significantly across 3 age groups (18-24, 25-34, and ≥ 35 years). Compared with FF pairs, women from MF pairs had similar prevalences of MD but higher prevalences of AD, probably because of methodological differences between studies. The cooperation status of one twin was unrelated to cotwin MD, AAD, or AD.

Structural models were based on tetrachoric correlations and asymptotic weight matrices estimated by means of PRELIS 2.⁵³ Models were fit by means of weighted least-squares estimation with the program Mx.⁵⁴ We compared alternative models by means of the principle of parsimony; models with fewer parameters are preferable if they do not provide substantially worse fit. We operationalized parsimony by the Akaike information criterion statistic,⁵⁵ calculated as the likelihood-ratio χ^2 minus 2 times the *df*.

For this report, we conducted several analyses investigating potential effects of age heterogeneity, study differences, attrition, and pairwise completion on comorbidity. Significance was based on $P < .05$ for all analyses. To test for possible biases in estimated comorbidity due to incomplete ascertainment from age censoring, we used logistic regression to predict MD from alcohol diagnosis (AD or AAD), age at interview, and the interaction of age and alcohol diagnosis, separately for men and women. To test for age heterogeneity in cross-disorder cross-twin resemblance, complete pairs were divided into 15 groups of 3 age bands (19-29, 30-39, and ≥ 40 years) by 5 zygosity types. The fit of a model requiring the twin 1-twin 2, cross-disorder correlations to be equivalent across age groups was compared with the fit of a model allowing age group differences. Similarly, we tested for differences in comorbidity

by pair completion status by comparing the fit of a model requiring twins from incomplete pairs to have diagnostic prevalences and MD-AD (or MD-AAD) correlations equal to those among complete pairs, to the fit of a model allowing differences by completion status.

MODELS FOR COMORBIDITY

We fit a series of models to the twin-pair correlation matrices to test a priori hypotheses about the covariation in liability to depression and alcoholism. These hypotheses were as follows: no depression-alcoholism covariation (either within-person or cross-twin) (model i), no cross-twin covariation (model ii), and no cross-twin covariation in opposite-sex pairs (model iii). The fit of these models was compared with that of a standard baseline model requiring equal within-person depression-alcoholism correlations within sexes regardless of zygosity, and, for same-sex pairs, equal cross-twin correlations (ie, twin 1 depression-twin 2 alcoholism correlation equals the twin 2 depression-twin 1 alcoholism correlation).

We then fit models to evaluate the adequacy of 3 explanations for how comorbidity arises and 2 hypotheses related to sex differences:

1. Phenotypic comorbidity posits that the risk of alcoholism in the relatives of individuals with depression is increased only if the relatives also have depression. We fit a strong version of this hypothesis, that there is no resemblance for alcoholism except that mediated through risk for depression (Figure 2, A). We also tested the same model for the reverse hypothesis (not pictured): that familial resemblance for depression is mediated through familial risk for alcoholism.

2. Comorbidity arising from common liability posits that alcoholism and depression co-occur in families because they have the same underlying causes. The familial basis for the two disorders is identical; individual-specific processes determine which disorder is manifest (Figure 2, B).

3. Comorbidity arising from correlated liability posits that alcoholism and depression co-occur in families because the contributing factors are correlated. There are genetic and environmental factors that contribute to both disorders, as well as factors specific to each disorder (Figure 2, C).

4. Sex differences in sources of comorbidity are indicated if the cross-twin alcoholism-depression correlation is smaller for opposite-sex than for same-sex DZ pairs. If men and women have completely separate sources of comorbidity, these correlations will be 0 in opposite-sex pairs.

5. Sex-dependent expression is when the same liability has different manifestations in men and women. If male alcoholism and female depression have common causes, they should be more strongly associated than male depression with female alcoholism.

ciations were attenuated when comorbidity in the probands and relatives was taken into account.

A second limitation is that family studies cannot distinguish whether vulnerability is transmitted through genetic or environmental means. The results from genetically informative studies of comorbidity are mixed. Three clinically based twin studies suggest that depression and alcoholism are transmitted independently.²⁶⁻²⁸

A previous analysis of the female-female twins from the current (epidemiologically based) sample found overlapping liability for MD and AD and attributed most of this to genetic factors shared by the two disorders.²⁹ Of 4 adoption studies, 2 found weak evidence of increased depression among adopted-away children of alcoholic parents,^{30,31} 1 found no increased depression,³² and another found increased alcoholism^{33,34} among biological rela-

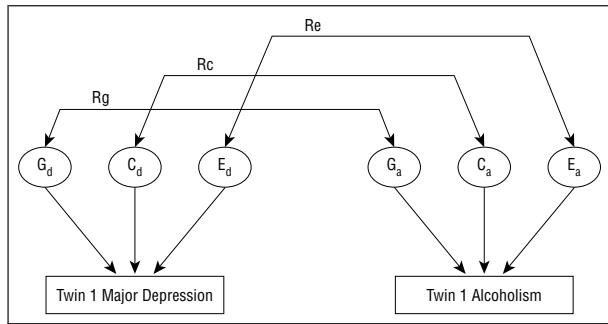


Figure 1. Schematic model for the within-person correlation between major depression (d) and liability to alcohol dependence (a). Three latent sources contribute to the risk for each disorder: additive genetic factors (G), common environments shared by members of a twin pair (C), and individual-specific environmental factors (E). Comorbidity arises because the sources underlying each disorder are correlated (indicated by double-headed arrows [Rg, Rc, Re]). The magnitude of these correlations may differ for males and females.

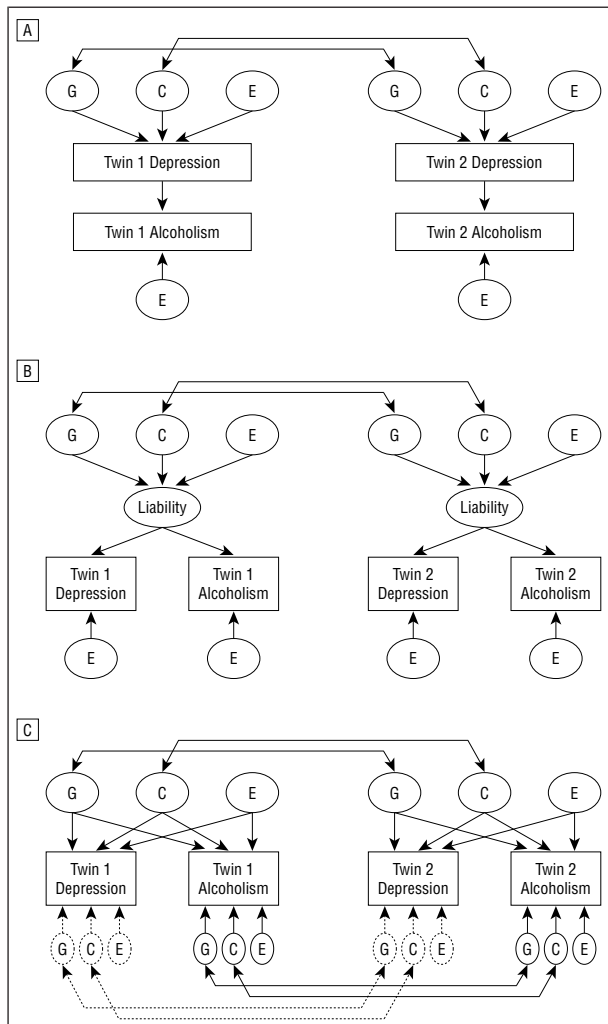


Figure 2. Schematic models for alternative explanations for comorbidity. A, Phenotypic comorbidity model in which familial resemblance for alcoholism arises solely from familial resemblance for depression. B, Common liability model in which familial resemblance for the disorders comes from the same genetic and familial environmental sources. C, Correlated liability model in which the sources of liability are overlapping but not identical. Not all factors shown can be identified when only 2 disorders are studied. Dotted lines indicate factors not included in the current analyses. These 3 models are distinguishable because they make different predictions about the degree of depression-alcoholism overlap in different twin-pair types. See the legend to Figure 1 for explanation of abbreviations.

tives of depressed adoptees. Goodwin et al³⁵ reported increased depression in the daughters of alcoholics only when they were raised by alcoholic adoptive parents, suggesting a possible gene by environment interaction. A final limitation of the existing literature is insufficient power to address potential sex effects.

We address these issues by studying the causes of comorbidity of major depression and alcoholism in a large, epidemiologically based twin sample unselected for history of depression or alcoholism.

RESULTS

ASSOCIATIONS OF SEX, AGE, STUDY, ATTRITION, AND PAIR STATUS WITH PREVALENCES AND COMORBIDITY

We observed substantial sex differences in prevalences, with MD being more common in women ($\chi^2_1=111, P<.001$) and alcohol disorders more prevalent in men (AD, $\chi^2_1=378, P<.001$; AAD, $\chi^2_1=524.6, P<.001$; **Table 1**). Among comorbid individuals, 61% of men reported that their alcoholism preceded depression, whereas 68% of women reported that depression began first ($\chi^2_1=9.5, P=.002$). Onset of MD was significantly earlier among comorbid individuals than among subjects with MD alone. Onset of MD tended to be later in comorbid women than in those with AD alone, but there was no difference among men.

We found no evidence of biases associated with study, age, attrition, or pair status. Age did not interact with alcohol diagnosis in predicting risk for MD. Women from MM/MF and FF studies did not differ in degree of comorbidity. The twin 1–twin 2, cross-disorder correlation did not differ across age groups. The FF participants not included in the current interview did not differ from included subjects in prevalences of MD or AD at previous assessments. Twins from complete and incomplete pairs did not differ in prevalences or comorbidity.

PAIR SIMILARITY AND MODEL FITTING

Pair resemblance for MD and various definitions of alcoholism was consistently stronger among MZ pairs than same-sex and opposite-sex DZ pairs (**Table 2**). The degree of comorbidity was modest; the within-person correlations between MD and alcohol diagnoses ranged from 0.24 to 0.31 among men and 0.29 to 0.37 among women. The key information for uncovering the sources of comorbidity is contained in the cross-twin cross-disorder correlations. These were modest in all pairs, although highest for MZ pairs, followed by same-sex DZ pairs, and lowest for opposite-sex pairs. Excluding secondary cases of AD did not appreciably change the estimates. Therefore, we present model-fitting results for MD with AD and AAD.

As expected, the model of no MD-AD covariation fit poorly (model i in **Table 3**). Allowing within-person covariation (model ii) improved the fit, but it was still substantially worse than the baseline model fit. Allowing MD-AD covariation only in same-sex pairs (model

Table 1. Lifetime Prevalence of DSM-III-R Major Depression, Alcohol Abuse, and Alcohol Dependence Among 8733 Adult Twins*

	Males (n = 5081)			Females (n = 3652)		
	No. (%)	Onset Age, Mean (±SD), y		No. (%)	Onset Age, Mean (±SD), y	
		MD	AA or AD		MD	AA or AD
Major depression (MD) only	746 (14.7)	24.7 ± 10.2†	NA	1157 (31.7)	24.8 ± 9.6‡	NA
Alcohol dependence (AD) only	810 (15.9)	NA	20.8 ± 5.3	138 (3.8)	NA	20.1 ± 4.9§
Alcohol abuse (AA) only	286 (5.6)	NA	21.4 ± 6.1	68 (1.9)	NA	20.8 ± 5.6
MD and AD	634 (12.5)	22.4 ± 9.9	21.0 ± 6.0	270 (7.4)	21.0 ± 9.1	21.9 ± 6.6
MD and AA	119 (2.3)	24.3 ± 9.6	22.1 ± 5.8	46 (1.3)	23.6 ± 9.0	21.5 ± 5.8
No MD, AD, or AA diagnosis	2486 (48.9)	NA	NA	1973 (54.0)	NA	NA

*Alcohol dependence is with or without abuse; alcohol abuse is without dependence. NA indicates not applicable.

†Differs from comorbid MD: $t_{1496} = 15.3$, $P < .001$, $R^2 = 1.0\%$.

‡Differs from comorbid MD: $t_{1470} = 32.1$, $P < .001$, $R^2 = 2.1\%$.

§Differs from comorbid AD: $t_{521} = 7.5$, $P < .05$, $R^2 = 0.7\%$.

Table 2. Tetrachoric Correlations (and 95% Confidence Intervals) for Within-Person and Cross-Twin Lifetime DSM-III-R Major Depression, Alcohol Use Disorders, and Their Covariation*

	Within-Person Correlations		Cross-Twin Correlations					
	Males (n = 4430)	Females (n = 3080)	Males MZ (n = 862)	Male DZ (n = 649)	Female MZ (n = 506)	Female DZ (n = 330)	Opposite-Sex DZ (n = 1408)	
MD	NA	NA	0.31 (0.20 to 0.42)	0.11 (-0.02 to 0.24)	0.40 (0.28 to 0.53)	0.13 (-0.04 to 0.30)	0.11 (0.02 to 0.19)	
AD	NA	NA	0.49 (0.40 to 0.59)	0.26 (0.13 to 0.39)	0.64 (0.48 to 0.80)	0.06 (-0.25 to 0.36)	0.14 (0.03 to 0.24)	
Nonsecondary AD†	NA	NA	0.47 (0.37 to 0.57)	0.23 (0.10 to 0.36)	0.61 (0.43 to 0.79)	0.08 (-0.23 to 0.39)	0.14 (0.03 to 0.25)	
AAD	NA	NA	0.54 (0.45 to 0.63)	0.34 (0.22 to 0.45)	0.53 (0.36 to 0.69)	0.13 (-0.14 to 0.39)	0.11 (0.01 to 0.21)	
							Male MD–Female ALC	
MD with AD‡	0.31 (0.26 to 0.36)	0.37 (0.30 to 0.44)	0.20 (0.11 to 0.28)	0.09 (-0.01 to 0.18)	0.20 (0.07 to 0.32)	0.07 (-0.09 to 0.23)	-0.04 (-0.15 to 0.07)	Female MD–Male ALC 0.04 (-0.05 to 0.13)
MD with nonsecondary AD†‡	0.24 (0.19 to 0.29)	0.29 (0.22 to 0.37)	0.21 (0.13 to 0.30)	0.09 (-0.01 to 0.18)	0.15 (0.02 to 0.27)	0.05 (-0.11 to 0.21)	-0.04 (-0.15 to 0.08)	0.04 (-0.05 to 0.13)
MD with AAD‡	0.29 (0.24 to 0.34)	0.31 (0.24 to 0.37)	0.21 (0.13 to 0.29)	0.03 (-0.06 to 0.13)	0.19 (0.08 to 0.31)	0.09 (-0.06 to 0.24)	0.04 (-0.06 to 0.14)	0.00 (-0.08 to 0.09)

*MD indicates major depression; AD, alcohol dependence; AAD, alcohol abuse or dependence; ALC, AD or AAD; MZ, monozygotic; DZ, dizygotic; and NA, not applicable.

†N = 854 (MZ males), 646 (DZ males), 506 (MZ females), 330 (DZ females), and 1403 (opposite-sex DZ).

‡Correlations were estimated using equality constraints, eg, for same-sex pairs, the correlation of twin1 MD with twin2 AD is constrained to equal the correlation of twin2 MD with twin1 AD.

iii) resulted in a fit not distinguishable from the baseline model, indicating that the cross-sex MD-AD correlations did not differ from 0.

The phenotypic comorbidity models (Figure 2, A) fit the data poorly, both the one requiring relative resemblance for AD arising from familial resemblance for MD (model 1) and the one requiring resemblance for MD arising from AD (model 1a). The common-liability model (Figure 2, B) also fits poorly (model 2). In contrast, the correlated-liability model (Figure 2, C) fits well (model 3). Requiring the cross-sex MD-AD correlations to be 0 changed the fit minimally (model 4), indicating different sources of the MD-AD association for men and women. Since these correlations do not differ from 0, we did not test whether the female

depression–male alcoholism association differs from that for female alcoholism with male depression.

On the basis of the results of model 3, a reduced model (3a) was fit in which all near-0 parameters were dropped. For AD, all common environment parameters could be equated to 0 with no loss of fit. On the basis of this “best-fitting” model, the MD-AD correlation for men was $r=0.31$, and for women, $r=0.37$ (Table 4, Figure 3). For both sexes, genetic factors were significant, accounting for 61% of this association in men and 51% in women. The remaining association was due to individual-specific sources. The large SEs around these estimates reflect the lack of precision with dichotomous categories even with large samples.

Table 3. Goodness-of-Fit Results From Models for Comorbidity of Lifetime *DSM-III-R* Major Depression With Alcoholism*

Model	Description	Model Fit				
		df	MD and AD		MD and AAD	
			χ^2	AIC	χ^2	AIC
Models Testing Magnitude of Comorbidity						
B	Baseline model	32	15.5	-48.5	14.3	-49.7
i	No MD-ALC covariance	40	292.6	212.6	254.2	174.2
ii	No cross-twin MD-ALC covariance	38	50.6	-25.4	54.0	-22.0
iii	Opposite-sex cross-twin covariance = 0	34	15.7	-52.3	16.0	-52
Models Testing Sources of Comorbidity						
1	Phenotypic comorbidity, ALC is secondary to MD	38	119.1	35.1	122.7	38.7
1a	Phenotypic comorbidity, MD is secondary to ALC	38	74.9	-9.1	82.2	-1.8
2	Common liability	41	60.5	-21.5	62.8	-19.2
3	Correlated liability within and across sexes	34	20.5	-47.5	20.4	-47.6
4	Correlated liability within sexes, no cross-sex MD-ALC covariance	34	21.4	-46.6	20.1	-47.9
3a	Best-fitting reduced model†	40	20.5	-59.5	19.9	-60.1

*MD indicates major depression; AD, alcohol dependence; AAD, alcohol abuse or dependence; ALC, AD or AAD; AIC, Akaike information criterion.
 †AD: no common environment effects; AAD: no common environment except specific AAD in males (df = 39).

Table 4. Parameter Estimates and 95% Confidence Intervals From Correlated Liability Models for the Comorbidity of Major Depression With Alcoholism

Model	Sex	Within-Person Sources for Depression-Alcoholism Comorbidity			
		Total	Additive Genetic	Common Environment	Specific Environment
Major Depression With Alcohol Dependence					
(3) Full model	Male	0.31 (0.26-0.36)	0.17 (0.00-0.26)	0.01 (0.00-0.17)	0.13 (0.04-0.21)
	Female	0.37 (0.31-0.44)	0.19 (0.00-0.30)	0.00 (0.00-0.10)	0.18 (0.07-0.29)
(3a) Reduced model	Male	0.31 (0.26-0.36)	0.19 (0.11-0.26)	Fixed at 0	0.12 (0.05-0.20)
	Female	0.37 (0.30-0.44)	0.19 (0.08-0.30)	Fixed at 0	0.18 (0.07-0.29)
Major Depression With Alcohol Abuse/Dependence					
(3) Full model	Male	0.29 (0.24-0.33)	0.19 (0.05-0.26)	0.00 (0.00-0.10)	0.10 (0.03-0.18)
	Female	0.31 (0.24-0.37)	0.18 (0.07-0.29)	0.00 (0.00-0.07)	0.13 (0.01-0.23)
(3a) Reduced model	Male	0.29 (0.25-0.34)	0.18 (0.11-0.26)	Fixed at 0	0.11 (0.04-0.18)
	Female	0.31 (0.24-0.37)	0.18 (0.07-0.29)	Fixed at 0	0.13 (0.02-0.24)

The pattern of results was the same for AAD as for AD. The best-fitting model included marginally significant residual C variation on AAD in men, but there was no evidence of common environmental contributions to the comorbidity of MD and AAD.

COMMENT

Our results suggest that sex-specific processes contribute to the lifetime comorbidity of depression and alcoholism. These results may help explain the lack of consistency in the results from previous studies, in which there was usually inadequate power to test for sex-specific transmission. We were able to detect these effects because we used a twin design with a large number of opposite-sex pairs.

Our results are most consistent with an explanation for comorbidity in which the causes of depression and alcoholism are overlapping but not isomorphic. There are genetic and specific environmental factors that influence both disorders and influences specific to each dis-

order. The overlap accounts for a relatively small proportion of the variation in liability to these disorders; the correlations of 0.29 to 0.37 translate into overlaps of 9% to 14%. Of this overlap, 50% to 60% is attributed to shared genetic factors and the remainder to specific environmental influences. We found no evidence that common environmental factors contribute to alcoholism-depression comorbidity.

The results do not support a causal model of phenotypic vulnerability in which depression causes alcoholism or alcoholism causes depression, and familial resemblance for the secondary disorder arises only from familial transmission of the first. However, there are less restrictive variations on the phenotypic model that cannot be rejected in our data. For example, a phenotypic model of MD secondary to AD that allowed residual familial resemblance for MD is mathematically similar to our correlated-liability model. The two models can be distinguished only if the pattern of genetic and environmental effects for comorbidity are disproportional to those influencing AD. In our data, these effects are close to pro-

portional and the MD-AD overlap is modest, so we cannot distinguish these possibilities.

One explanation for sex differences in prevalences of depression and alcoholism is sex-limited gene expression, in which the disorders have shared liability that combines with sex-specific biological or social factors to give rise to either alcoholism or depression. This could arise if males are shaped by social factors to develop drinking problems rather than to express their depressive tendencies. Studies of ethnic groups in which heavy drinking is discouraged, such as in Israel⁵⁶ and among the Old Order Amish,⁵⁷ provide indirect support for this hypothesis, because the men have low prevalences of alcoholism and prevalences of depression similar to those of women. This explanation is a variant of the common-liability model (Figure 2, B) and so is inconsistent with our data. However, if depression or alcoholism arises from the interaction of genetic liability with sex-specific genetic or environmental factors, the pattern of twin correlations would be similar to those we observed, with the cross-twin depression-alcoholism association in opposite-sex pairs indistinguishable from 0.

Although the phenotypic (within-person) correlation of MD with AAD was lower than for MD with AD, the estimated genetic overlap of AAD with MD was the same as for AD, suggesting that alcohol abuse also shares genetic liability with MD.

Our ability to test whether “secondary” alcoholism has a different cause was limited, as only approximately 10% of cases of AD in women and approximately 5% in men were secondary to MD. Exclusion of secondary cases of alcoholism reduced the association of depression and alcoholism within individuals, but not across twin pairs, consistent with secondary alcoholism being no less associated with familial MD. These findings are consistent with those of Schuckit et al,⁵⁸ who found that alcoholics with independent MD did not differ in family history of depressive disorder from those whose MD was secondary to their alcoholism. Similarly, Andrew et al¹⁵ found that twin pairs concordant for MD had (nonsignificantly) higher rates of alcoholism in their relatives than discordant pairs, inconsistent with a separate cause for “pure” MD. Comorbidity may have different implications depending on proband sex and family history²⁴ or may indicate greater liability. In our sample, individuals who had MD plus AD had significantly earlier onset of MD than depressed individuals without alcoholism, suggesting greater severity.

One study limitation is that subjects were white twins born in Virginia, so the results may not be generalizable to individuals from other regions or ethnic backgrounds. Our tests for biases associated with sample, age, completion status, and attrition suggest that restricting the modeling to subjects from complete pairs with complete data is not likely to have biased our results. However, other biases are possible.

Our prevalences of depression and alcoholism are somewhat higher than those reported for white adults in some US epidemiological studies, but the degree of comorbidity is similar to that in both US^{3,59} and international⁶⁰ studies. It could be that our methods result in a somewhat lower threshold for caseness. Use of a more

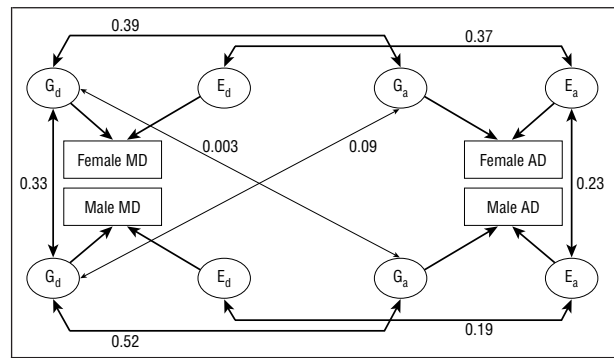


Figure 3. Estimated correlations among the additive genetic (G) and specific environmental (E) components underlying major depression (MD, d) and alcohol dependence (AD, a) based on the best-fitting model (model 3a in Table 3). The heavy lines indicate associations significantly greater than 0. The correlations between the genetic factors contributing to MD and the genetic factors for AD are as follows: $r = 0.39$ (95% confidence interval, 0.02–0.65) for females and $r = 0.52$ (95% confidence interval, 0.32–0.99) for males. The cross-sex, MD-AD genetic correlations do not differ from 0. By contrast, the corresponding value for these correlations in same-sex dizygotic pairs (not shown) are $r = 0.20$ for females and $r = 0.26$ for males. The remaining comorbidity is due to within-person environmental sources. These are correlated more strongly in females ($r = 0.37$) than males ($r = 0.19$). Estimates from common environmental sources did not differ from 0 and are not portrayed.

stringent definition (4 of 9 symptoms for DSM-III-R alcohol dependence and 6 of 9 for DSM-III-R major depression) produced prevalences more similar to those of US studies but produced minimal changes to MD-AD comorbidity, as indicated by within-person and cross-twin correlations. Thus, even if we used more narrow definitions, we would still obtain the same pattern of results.

Some subjects were still within the risk period for developing MD and AAD when interviewed. This censoring probably has less effect than in family studies, since twins are matched for age. Furthermore, we found no age-related differences in within-person or cross-twin MD-AD covariation. Because there are sex differences in the sequencing and onset ages of these disorders, it is possible that subsequent follow-up of this relatively young sample might result in a stronger cross-sex alcoholism-depression association. Although this association did not differ significantly across age groups, there was a trend in the predicted direction: the male AD–female MD correlation among opposite-sex pairs older than 40 years was $r = 0.17$ (95% confidence interval, 0.02 to 0.32), compared with the correlation of $r = -0.01$ (95% confidence interval, -0.04 to 0.09) among younger pairs.

Our classification of comorbid cases into secondary and nonsecondary alcoholism was based on the timing of episodes and may not correspond to what is etiologically primary. Our models are based on lifetime comorbidity of these disorders. Studies that examine the simultaneous occurrence of these disorders may find greater overlap in causes.

The models we used assume that the constructs of alcoholism and depression apply equally to men and women and to individuals with or without comorbidity. It is possible that our finding of a weaker association between alcoholism and depression in opposite-sex than in same-sex pairs is due to sex differences in measurement or clinical manifestations, rather than in causes.

Despite these limitations, this sample arguably provides the best genetically informative data from which to generalize about the causes of comorbidity of alcoholism and depression. Our findings of differences in men and women in the causes of comorbidity warrant further investigation of these complex processes.

Accepted for publication April 11, 2000.

Data collection was supported by grants R01-MH-AA-49492 and R01-AA/DA-09095 from the National Institutes of Health, Bethesda, Md. The preparation of the manuscript was supported by K01-AA-00236 and K05-MH-01277 from the National Institutes of Health.

The Virginia Twin Registry (now the Mid-Atlantic Twin Registry) was founded by Walter Nance, MD, and Linda Corey, PhD, in the Department of Human Genetics, Medical College of Virginia of Virginia Commonwealth University, Richmond, and is directed by Dr Corey and Lenn Murrelle, PhD. Sarah Woltz, MA, Frank Butera, MS, Lisa Halberstadt, MS, Barbara Brooke, MSW, and Patsy Waring supervised data collection. Charles O. Gardner, Jr, PhD, J. J. McArdle, PhD, and Michael C. Neale, PhD, provided statistical advice.

Preliminary versions of these analyses were presented at meetings of the Research Society on Alcoholism, Santa Barbara, Calif, June 1999, and the Behavior Genetics Association, Vancouver, British Columbia, July 1999.

Reprints: Carol A. Prescott, PhD, VIPBG, MCV/VCU, PO Box 980126, Richmond, VA 23298-0126 (e-mail: cprescott@hsc.vcu.edu).

REFERENCES

- Merikangas KR, Gelernter CS. Comorbidity for alcoholism and depression. *Psychiatr Clin North Am.* 1990;13:613-632.
- Boyd JH, Weissman MM. Epidemiology of affective disorders: a reexamination and future directions. *Arch Gen Psychiatry.* 1981;38:1039-1046.
- Kessler RC, McGonagle KA, Zhao S, Nelson CB, Hughes M, Eshleman S, Wittchen H-U, Kendler KS. Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States: results from the National Comorbidity Survey. *Arch Gen Psychiatry.* 1994;51:8-10.
- Regier DA, Farmer ME, Rae DS, Locke BZ, Keith SJ, Judd LL, Goodwin FK. Comorbidity of mental disorders with alcohol and other drug abuse: results from the epidemiologic catchment area (ECA) study. *JAMA.* 1990;264:2511-2518.
- Mueller TI, Lavori PW, Keller MB, Swartz A, Warshaw M, Hasin D, Coryell W, Endicott J, Rice J, Akiskal H. Prognostic effect of the variable course of alcoholism on the 10-year course of depression. *Am J Psychiatry.* 1994;151:701-706.
- Cloninger CR, Rice J, Reich T. Multifactorial inheritance with cultural transmission and assortative mating, II: a general model of combined polygenic and cultural inheritance. *Am J Hum Genet.* 1979;31:176-198.
- Cloninger CR, Reich T, Wetzell R. Alcoholism and affective disorders: familial associations and genetic models. In: Cloninger CR, Reich T, Wetzell R, eds. *Alcoholism and Affective Disorders: Clinical, Genetic and Biochemical Studies.* New York, NY: Spectrum Publications; 1979:57-86.
- Angst J. Zur Aetiologie und Nosologie endogener depressiver Psychosen. *Monogr Gesamtgeb Neurol Psychiatr.* 1966;112:1-118.
- Schuckit MA. Genetic and clinical implications of alcoholism and affective disorder. *Am J Psychiatry.* 1986;143:140-147.
- Gershon ES, Hamovitz J, Guroff JJ, Dibble E, Leckman JF, Sceery W, Targum SD, Nurnberger JI, Goldin LR, Bunney WE. A family study of schizoaffective, bipolar I, bipolar II, unipolar, and normal control probands. *Arch Gen Psychiatry.* 1982;39:1157-1167.
- Weissman MM, Gershon ES, Kidd KK, Prusoff BA, Leckman JF, Dibble E, Hamovitz J, Thompson WD, Pauls DL, Guroff JJ. Psychiatric disorders in the relatives of probands with affective disorders: the Yale University National Institute of Mental Health Collaborative Study. *Arch Gen Psychiatry.* 1984;41:13-21.
- Merikangas KR, Leckman JF, Prusoff BA, Pauls DL, Weissman MM. Familial transmission of depression and alcoholism. *Arch Gen Psychiatry.* 1985;42:367-372.
- Winokur G, Cadoret RJ, Dorzab J, Baker M. Depressive disease: a genetic study. *Arch Gen Psychiatry.* 1971;24:135-144.
- Winokur G, Coryell W. Familial alcoholism in primary unipolar major depressive disorder. *Am J Psychiatry.* 1991;148:184-188.
- Andrew M, McGuffin P, Katz R. Genetic and non-genetic subtypes of major depressive disorder. *Br J Psychiatry.* 1998;173:523-526.
- Coryell W, Winokur G, Keller M, Scheffner W, Endicott J. Alcoholism and primary major depression: a family study approach to co-existing disorders. *J Affective Disord.* 1992;24:93-99.
- Cadoret R, Winokur G. Depression in alcoholism. *Ann N Y Acad Sci.* 1974;233:34-39.
- Hasegawa K, Mukasa H, Nakazawa Y, Kodama H, Nakamura K. Primary and secondary depression in alcoholism: clinical features and family history. *Drug Alcohol Depend.* 1991;27:275-281.
- Leibenluft E, Madden PA, Dick SE, Rosenthal NE. Primary depressives with secondary alcoholism compared with alcoholics and depressives. *Compr Psychiatry.* 1993;34:83-86.
- O'Sullivan KB, Daly MM, Carroll BM, Clare AW, Cooney JG. Alcoholism and affective disorder among patients in a Dublin hospital. *J Stud Alcohol.* 1979;40:1014-1021.
- Schuckit M. Alcoholic patients with secondary depression. *Am J Psychiatry.* 1983;140:711-714.
- Berkson J. Limitations of the application of fourfold table analysis to hospital data. *Biometrics Bull.* 1946;2:47-53.
- Grant BF, Hasin DS, Dawson DA. Relationship between DSM-IV alcohol use disorders and DSM-IV major depression: examination of the primary-secondary distinction in a general population sample. *J Affective Disord.* 1996;38:113-128.
- Dawson DA, Grant BF. Family history of alcoholism and gender: their combined effects on DSM-IV alcohol dependence and major depression. *J Stud Alcohol.* 1998;59:97-106.
- Kendler KS, Davis CG, Kessler RC. The familial aggregation of common psychiatric and substance use disorders in the National Comorbidity Survey: a family history study. *Br J Psychiatry.* 1997;170:541-548.
- Kajij L. *Alcoholism in Twins.* Stockholm, Sweden: Almqvist & Wiksell; 1960.
- Mullan MJ, Gurling HMD, Oppenheim BE, Murray RM. The relationship between alcoholism and neurosis: evidence from a twin study. *Br J Psychiatry.* 1986;148:435-441.
- Gurling HMD, Oppenheim BE, Murray RM. Depression, criminality and psychopathology associated with alcoholism: evidence from a twin study. *Acta Genet Med Gemellol.* 1984;33:333-339.
- Kendler KS, Heath AC, Neale MC, Kessler RC, Eaves LJ. Alcoholism and major depression in women: a twin study of the causes of comorbidity. *Arch Gen Psychiatry.* 1993;50:690-698.
- Cadoret RJ, Cain CA, Grove WM. Development of alcoholism in adoptees raised apart from alcoholic biologic relatives. *Arch Gen Psychiatry.* 1980;37:561-563.
- von Knorring AL, Cloninger CR, Bohman M, Sigvardsson S. An adoption study of depressive disorders and substance abuse. *Arch Gen Psychiatry.* 1983;40:943-950.
- Goodwin DW, Schulsinger R, Hermansen L, Guze SB, Winokur G. Alcohol problems in adoptees raised apart from alcoholic biological parents. *Arch Gen Psychiatry.* 1973;28:238-255.
- Ingraham LJ, Wender PH. Risk for affective disorder and alcohol and other drug abuse in the relatives of affectively ill adoptees. *J Affective Disord.* 1992;26:45-52.
- Wender PH, Kety SS, Rosenthal D, Schulsinger F, Ortmann J, Lunde I. Psychiatric disorders in the biological and adoptive families of adopted individuals with affective disorders. *Arch Gen Psychiatry.* 1986;43:923-929.
- Goodwin DW, Schulsinger F, Knop J, Mednick S, Guze SB. Alcoholism and depression in adopted-out daughters of alcoholics. *Arch Gen Psychiatry.* 1977;34:751-755.
- Kendler KS, Prescott CA. Cannabis use, abuse and dependence in a population-based sample of female twins. *Am J Psychiatry.* 1998;155:1016-1022.
- Kendler KS, Prescott CA. A population-based twin study of lifetime major depression in men and women. *Arch Gen Psychiatry.* 1999;56:39-44.
- Prescott CA, Aggen SH, Kendler KS. Sex differences in the sources of genetic liability to alcohol abuse and dependence in a population based sample of U.S. twins. *Alcohol Clin Exp Res.* 1999;23:1136-1144.
- Kendler KS, Neale MC, Kessler RC, Heath AC, Eaves LJ. A population-based twin study of major depression in women: the impact of varying definitions of illness. *Arch Gen Psychiatry.* 1992;49:257-266.
- Spitzer RL, Williams JBW. *Structured Clinical Interview for DSM-III-R (SCID).* New York: Biometrics Research Dept, New York State Psychiatric Institute; 1985.
- Bucholz KK, Cadoret RJ, Cloninger CR, Dinwiddie SH, Hesselbrock VM, Nurn-

- berger JI Jr, Reich T, Schmidt I, Schuckit MA. A new, semi-structured psychiatric interview for use in genetic linkage studies: a report on the reliability of the SSAGA. *J Stud Alcohol*. 1994;55:149-158.
42. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition*. Washington, DC: American Psychiatric Association; 1987.
 43. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*. Washington, DC: American Psychiatric Association; 1994.
 44. Kendler KS, Heath AC, Neale MC, Kessler RC, Eaves LJ. A population-based twin study of alcoholism in women. *JAMA*. 1992;268:1877-1882.
 45. Prescott CA, Neale MC, Corey LA, Kendler KS. Predictors of problem drinking and alcohol dependence in a population-based sample of female twins. *J Stud Alcohol*. 1997;58:167-181.
 46. Prescott CA, Kendler KS. Genetic and environmental contributions to alcohol abuse and dependence in a population-based sample of male twins. *Am J Psychiatry*. 1998;156:34-40.
 47. Prescott CA, Kendler KS. Age at first drink and risk for alcoholism: a noncausal association. *Alcohol Clin Exp Res*. 1999;23:101-107.
 48. Falconer DS. The inheritance of liability to certain diseases, estimated from the incidence among relatives. *Ann Hum Genet*. 1965;29:51-76.
 49. Galbaud du Fort G, Bland RC, Newman SC, Boothroyd LJ. Spouse similarity for lifetime psychiatric history in the general population. *Psychol Med*. 1998;28:789-803.
 50. Merikangas KR. Assortative mating for psychiatric disorders and psychological traits. *Arch Gen Psychiatry*. 1982;39:1173-1180.
 51. Kendler KS, Neale MC, Heath AC, Kessler RC, Eaves LJ. A twin-family study of alcoholism in women. *Am J Psychiatry*. 1994;151:707-715.
 52. Maes HHM, Neale MC, Kendler KS, Hewitt JK, Silberg JL, Foley DL, Meyer JM, Rutter M, Simonoff E, Pickles A, Eaves LJ. Assortative mating for major psychiatric diagnoses in two population-based samples. *Psychol Med*. 1998;28:1389-1401.
 53. Joreskog K, Sorbom D. *PRELIS 2: User's Reference Guide*. Chicago, Ill: Scientific Software International; 1996.
 54. Neale MC. *Statistical Modelling With Mx*. Richmond: Dept of Psychiatry, Medical College of Virginia of Virginia Commonwealth University; 1991.
 55. Akaike H. Factor analysis and AIC. *Psychometrika*. 1987;52:317-332.
 56. Levav I, Kohn R, Dohrenwend BP, Shrout PE, Skodol AE, Schwartz S, Link BG, Naveh G. An epidemiological study of mental disorders in a 10-year cohort of young adults in Israel. *Psychol Med*. 1993;23:691-707.
 57. Egeland JA, Hostetter AM. Amish Study, I: affective disorders among the Amish, 1976-1980. *Am J Psychiatry*. 1983;140:56-61.
 58. Schuckit MA, Tipp JE, Bergman BA, Reich W, Hesselbrock VM, Smith TL. Comparison of induced and independent major depressive disorder in 2,945 alcoholics. *Am J Psychiatry*. 1997;154:948-957.
 59. Robins LN, Helzer JE, Przybeck TR. Alcohol disorders in the community: a report from the Epidemiologic Catchment Area. In: Rose RM, Barrett JE, eds. *Alcoholism: Origins and Outcome*. New York, NY: Raven Press Ltd; 1988:15-29.
 60. Helzer JE, Canino GJ, Hwu H-G, Bland RC, Newman S, Yeh E-K. Alcoholism: a cross-national comparison of population survey with the Diagnostic Interview Schedule. In: Rose RM, Barrett JE, eds. *Alcoholism: Origins and Outcome*. New York, NY: Raven Press Ltd; 1988:31-47.