ORIGINAL ARTICLE

Familial Transmission of Substance Dependence: Alcohol, Marijuana, Cocaine, and Habitual Smoking

A Report From the Collaborative Study on the Genetics of Alcoholism

Laura Jean Bierut, MD; Stephen H. Dinwiddie, MD; Henri Begleiter, MD; Raymond R. Crowe, MD; Victor Hesselbrock, PhD; John I. Nurnberger, Jr, MD, PhD; Bernice Porjesz, PhD; Marc A. Schuckit, MD; Theodore Reich, MD

Background: Alcoholism and substance dependence frequently co-occur. Accordingly, we evaluated the familial transmission of alcohol, marijuana, and cocaine dependence and habitual smoking in the Collaborative Study on the Genetics of Alcoholism.

Methods: Subjects (n = 1212) who met criteria for both *DSM-III-R* alcohol dependence and Feighner definite alcoholism and their siblings (n = 2755) were recruited for study. A comparison sample was also recruited (probands, n = 217; siblings, n = 254). Subjects were interviewed with the Semi-Structured Assessment for the Genetics of Alcoholism. The familial aggregation of drug dependence and habitual smoking in siblings of alcohol-dependent and non–alcohol-dependent probands was measured by means of the Cox proportional hazards model.

Results: Rates of alcohol, marijuana, and cocaine dependence and habitual smoking were increased in siblings of alcohol-dependent probands compared with siblings of controls. For siblings of alcohol-dependent probands, 49.3% to 50.1% of brothers and 22.4% to 25.0% of sisters were alcohol dependent (lifetime diagnosis), but this elevated risk was not further increased by comorbid substance dependence in probands. Siblings of marijuana-dependent probands had an elevated risk of developing marijuana dependence (relative risk [RR], 1.78) and siblings of cocaine-dependent probands had an elevated risk of developing cocaine dependence (RR, 1.71). There was a similar finding for habitual smoking (RR, 1.77 in siblings of habitual-smoking probands).

Conclusions: Alcohol, marijuana, and cocaine dependence and habitual smoking are all familial, and there is evidence of both common and specific addictive factors transmitted in families. This specificity suggests independent causative factors in the development of each type of substance dependence.

Arch Gen Psychiatry. 1998;55:982-988

IT HAS LONG BEEN recognized that family members of an alcohol-dependent individual are more likely to suffer from alcohol dependence.[1-4] Adoption and twin studies demonstrate that the familial aggregation of alcohol dependence is in part caused by genetic factors.[5-8] There is also evidence of increased familial aggregation of psychoactive drug abuse and dependence. Several studies have found increased rates of drug abuse and/or dependence in relatives of individuals dependent on opiates or cocaine compared with relatives of alcoholics or subjects from the general population.[9-14] A case-control study of adoptees separated at birth from their biological parents and differing by the presence or absence of drug abuse or dependence in their biological parents has demonstrated the importance of genetic factors in the development of substance dependence.[15] Twin studies that examined genetic influences of drug use disorder (defined as any illicit drug abuse or dependence) have found higher rates of concordance for drug use disorder among monozygotic twins than dizygotic twins.[16,17] These family, adoption, and twin studies support the familial transmission of alcohol and drug dependence and implicate genetic factors.

See also pages 964, 967, and 973

Epidemiological studies have shown that alcohol dependence is frequently com-

From the Departments of Psychiatry, Washington University School of Medicine, St Louis, Mo (Drs Bierut and Reich); Finch University of Health Sciences, The Chicago Medical School, North Chicago, Ill (Dr Dinwiddie); State University of New York Health Sciences Center at Brooklyn, Brooklyn, NY (Drs Begleiter and Porjesz); University of Iowa College of Medicine, Iowa City (Dr Crowe); University of Connecticut Health Center, Farmington, (Dr Hesselbrock); Indiana University School of Medicine, Indianapolis (Dr Nurnberger); and University of California–San Diego (Dr Schuckit).

This article is also available on our Web site: www.ama-assn.org/psych.

©1998 American Medical Association. All rights reserved.
Downloaded From: http://archpsyc.jamanetwork.com/ on 03/06/2015

SUBJECTS AND METHODS

Data presented are from the Collaborative Study on the Genetics of Alcoholism (COGA), a multisite family and genetic study of probands with alcohol dependence, their relatives, and control families. The 6 study sites are Indiana University, Indianapolis; State University of New York at Brooklyn; University of California–San Diego and Scripps Institute, San Diego; University of Connecticut, Farmington; University of Iowa, Iowa City; and Washington University, St Louis, Mo. Written informed consent was obtained from all subjects.

SUBJECTS

Subjects were identified from consecutive admissions to chemical dependency treatment settings that included both inpatient and outpatient units, and from publicly and privately funded centers. Of the subjects, 92.7% agreed to the initial screening protocol for the study.[21] Subjects were required to meet criteria for both *DSM-III-R* alcohol dependence[22] and Feighner definite alcoholism,[23] to be older than 17 years, to speak English, and to have at least 2 first-degree relatives living in one of the COGA catchment areas. Probands were excluded if they had life-threatening illness, severe cognitive impairment, acute psychosis, habitual intravenous drug use (>30 times lifetime or any intravenous drug use in the last 6 months), or human immunodeficiency virus infection. Of the screened subjects, 22.3% met these recruitment criteria. Participants were most often eliminated from the study because their biological relatives could not be recruited, as in cases of adoption, estrangement from families, or too few living relatives in a catchment area (52.9% of screened subjects). Of the eligible subjects, 40.0% agreed to participate and were identified as "COGA probands." All available first-degree family members of probands were then invited to participate in the study.

Control families were also recruited at each site, through random sampling of large families (5 family members or more). Each site chose its strategy of ascertainment, such as random consecutive sampling from health maintenance organizations, dental clinics, or driver's license bureaus, to select control probands and their first-degree relatives. Alcohol dependence, drug dependence, or another psychiatric disorder were not exclusionary criteria for control subjects.

To eliminate confounding factors associated with secular trends in drug use across generations, analyses in this article were limited to interviewed COGA (alcohol-dependent) probands, control probands, and their siblings. Data were available on 1212 COGA probands, 2755 COGA siblings, 217 control probands, and 254 control siblings.

ASSESSMENT

All subjects completed the Semi-Structured Assessment for the Genetics of Alcoholism,[24] a highly reliable, semistructured lay interview designed to assess alcohol abuse and dependence, other substance dependence, smoking, and related psychiatric disorders over a lifetime. Interview data were checked for consistency by an editor, entered into a computerized data file, screened by a data program for consistency, and included on a master data file. Psychiatric diagnoses were made by computer algorithm that analyzed the responses from the personal interview.

Alcoholism was defined in all subjects as meeting criteria for both *DSM-III-R* alcohol dependence and Feighner definite alcoholism. This definition was more stringent than *DSM-III-R* alcohol dependence alone; 90.0% of those who met criteria for *DSM-III-R* alcohol dependence met criteria for this combined alcoholism diagnosis. Diagnoses of marijuana and cocaine dependence were made by means of *DSM-III-R* criteria. Tobacco dependence was not evaluated in the initial assessment, so *habitual smoking,* defined as smoking at least 1 pack (20 cigarettes) daily for 6 months or more, was used as a proxy. Data used in these analyses were from the data file completed in December 1997.

ANALYSIS

The familial specificity of substance dependence in siblings of alcohol-dependent probands was examined by means of the Cox proportional hazards model,[25] a survival analysis that includes individuals who are not through the age of risk for developing the disorder. The effect of each predictor variable in a multivariate analysis is adjusted for the effects of every other predictor variable in the model. These analyses used the onset of marijuana and cocaine dependence as well as habitual tobacco smoking as outcome variables. Predictor variables were sibling characteristics (birth cohort, sex, race, study site, and other substance dependence) and proband characteristics (sex, habitual smoking, and alcohol, marijuana, and cocaine dependence). To study temporal trends of substance dependence, siblings were divided into 3 birth cohorts: those born before 1950, from 1950 to 1959, and in 1960 or later. This grouping divided the sample into approximately equal thirds.

Because multiple siblings from some families were ascertained, data from siblings were not truly independent observations, and thus SEs calculated in survival analyses may underestimate the true SEs. Therefore, 1000 "random" resampling bootstrap replications were performed on all survival analyses, ie, 1429 families (from 1212 COGA families and 217 control families) were randomly resampled with replacement, and Cox proportional hazards models were rerun. Standard deviations from these 1000 resampled estimates were used as the SE to estimate 95% confidence intervals.[26]

plicated by comorbid psychiatric disorders.[18] Among alcohol-dependent individuals, 47% have another mental disorder,[19] and a significant proportion of this comorbidity is accounted for by drug dependence.

Since alcohol and drug dependence are both familial and frequently comorbid, several groups have studied the cotransmission of alcohol and drug dependence in families.[9-13] The most comprehensive family study has examined relatives of opiate-dependent probands with and without alcohol dependence in addition to "normal" control probands.[12] That study showed increased rates of alcohol dependence in relatives of opiate-dependent probands after controlling for the presence of alcohol dependence in probands. This suggests that a common addictive

©1998 American Medical Association. All rights reserved.
Downloaded From: http://archpsyc.jamanetwork.com/ on 03/06/2015

Table 1. Demographic Characteristics and Lifetime Prevalences of Substance Dependence in Probands and Siblings*

	COGA Probands (n = 1212)	COGA Siblings (n = 2755)	Control Probands (n = 217)	Control Siblings (n = 254)
No. of subjects				
Men	916†	1197	111	111
Women	296†	1558	106	143
Age, y				
Mean ± SD	37.72 ± 10.62†	36.35 ± 9.52‡	34.57 ± 13.06	26.15 ± 6.62
Range	17-77	18-76	18-68	17-48
Race, %				
White	70.4† (14.5)	71.0§ (9.1)	83.0	79.9
African American	19.7† (20.7)	19.7‡ (27.5)	6.9	6.3
Hispanic	6.8	6.8	4.6	7.5
Other	3.1	2.5‡ (12.2)	5.5	6.3
Alcohol dependence, %				
Men	100.0† (843.8)	49.7‡ (36.4)	16.2	19.8
Women	100.0† (381.7)	23.8‡ (25.1)	3.8	6.0
Marijuana dependence, %				
Men	47† (55.1)	28.5‡ (16.1)	9.9	10.8
Women	40† (44.7)	11.6‖ (6.0)	4.7	4.9
Cocaine dependence, %				
Men	47† (75.9)	20.1‡ (16.2)	3.6	4.5
Women	51† (83.2)	11.2‡ (11.7)	0.9	2.1
Habitual smoking, %				
Men	63† (84.1)	41.6‡ (33.6)	18.0	13.5
Women	55† (58.1)	30.4‡ (27.3)	12.3	9.8

**COGA indicates Collaborative Study on the Genetics of Alcoholism. The χ^2 test with 1 df was used; χ^2 values for significant results are given in parentheses.*
†P<.001 vs control probands.
‡P<.001 vs control siblings.
§P<.01 vs control siblings.
‖P<.05 vs control siblings.

factor is transmitted in families. Other support of a common factor in the transmission of alcohol and drug use comes from a large study of male twins that demonstrated shared genetic factors that contributed to the development of both heavy alcohol use and smoking.[20]

In addition to evidence for a common addictive factor, several studies demonstrate a specific factor in the familial clustering of substance dependence.[9-12] However, the specificity of the transmission of dependence in families could not be further examined, since all drug dependence was collapsed into a single category.

The purpose of this study was to further examine whether there is only a general "addictive risk factor" for drug dependence that is transmitted in families. If there is only a nonspecific familial risk factor for drug dependence, one would expect relatives of those with a more severe addiction syndrome (eg, comorbid alcohol, marijuana, and cocaine dependence) to have elevated rates of alcohol dependence. Also, rates of other forms of dependence would also be elevated in a nonspecific fashion. To test the hypothesis of a general addictive tendency, we evaluated the familial aggregation of alcohol and drug dependence. The most common forms of dependence in this sample were studied—alcohol, marijuana, and cocaine dependence and habitual smoking—and the following questions were addressed: (1) Does the presence of comorbid marijuana and/or cocaine dependence in individuals with alcoholism influence the prevalence of alcohol dependence in their siblings? (2) Does having a sibling with alcohol dependence increase the risk of developing marijuana and cocaine dependence and habitual smoking, independent of the risk of developing alcoholism? (3) Is there any specificity in the familial transmission of substance dependence? If so, is the familial aggregation related only to exposure?

RESULTS

Table 1 details the demographic characteristics and substance dependence diagnoses. Rates of alcohol, marijuana, and cocaine dependence and habitual smoking were significantly increased in brothers and sisters of alcohol-dependent (COGA) probands compared with control siblings. Almost half (44.2%) of COGA siblings had a lifetime diagnosis of dependence, with alcohol dependence most common, affecting 79.3% of those siblings. Of COGA siblings, 18.9% had marijuana dependence compared with 7.5% of control siblings ($\chi^2_1 = 21$; $P<.001$), and 15.1% of COGA siblings had cocaine dependence compared with 3.1% of control siblings ($\chi^2_1 = 27$; $P<.001$). Habitual smoking was also increased in COGA siblings compared with control siblings (35.3% vs 11.4%; $\chi^2_1 = 64$; $P<.001$). Thus, having a sibling with alcohol dependence significantly increased an individual's risk of developing substance dependence.

Comorbid drug dependence was common in alcohol-dependent probands and siblings. An additional diagnosis of marijuana and/or cocaine dependence was found in 61.6% of COGA probands and in 49.8% of their alcohol-dependent siblings. Similarly, there were increased rates of comorbid marijuana and/or cocaine dependence in con-

©1998 American Medical Association. All rights reserved.
Downloaded From: http://archpsyc.jamanetwork.com/ on 03/06/2015

trol probands and siblings with alcohol dependence (45.5% and 26.7%, respectively).

To examine whether the risk of alcohol dependence in COGA siblings was affected by probands' comorbid substance dependence, COGA probands were subdivided into mutually exclusive groups by diagnosis: alcohol dependence only, alcohol and marijuana dependence, alcohol and cocaine dependence, and alcohol, marijuana, and cocaine dependence (**Table 2**). The risk of developing alcohol dependence in COGA siblings was not affected by comorbid substance dependence in COGA probands. Regardless of other substance dependence diagnoses for probands, 49.3% to 50.1% of brothers and 22.4% to 25.0% of sisters had a lifetime diagnosis of alcohol dependence. This result is not compatible with a model of familial transmission of a general addictive tendency in which a more severe form of dependence in probands (modeled as alcohol and comorbid drug dependence) conferred an increased risk to siblings for the development of alcohol dependence.

Table 2. Lifetime Prevalence of Alcohol Dependence in COGA Siblings by Proband Diagnosis*

	Siblings, % (No.†)	
Proband Diagnosis	**Men**	**Women**
Alcohol dependence	49.5 (412)	22.4 (532)
Alcohol dependence, marijuana dependence	49.3 (199)	24.0 (238)
Alcohol dependence, cocaine dependence	49.7 (183)	25.0 (288)
Alcohol dependence, marijuana dependence, cocaine dependence	50.1 (403)	24.6 (500)

*COGA indicates Collaborative Study on the Genetics of Alcoholism. Comparison of rates of alcohol dependence in siblings given proband diagnosis, separated by sex: men, P = .99, $\chi^2_3 = 0.051$; women, P = .80, $\chi^2_3 = 1.009$.

†Total number of siblings in that group.

Data were further examined to see whether increased rates of drug dependence and habitual smoking in siblings were mediated only through an increased rate of alcohol dependence. If this were the case, one would expect non–alcohol-dependent siblings to have the same rate of substance dependence regardless of the proband's comorbid diagnoses. By dividing COGA siblings into those with and without alcohol dependence, and as to whether probands had comorbid substance dependence, the interaction between alcohol dependence and other substance dependence was evaluated. As seen in **Table 3**, among alcohol-dependent siblings, siblings of COGA probands with comorbid marijuana dependence had about a 2-fold increase in the risk of marijuana dependence compared with siblings of COGA probands without marijuana dependence. Similarly, there was an increased rate of marijuana dependence among siblings without alcohol dependence if probands had comorbid marijuana dependence. This reached statistical significance for non–alcohol-dependent sisters, and a similar trend was seen in non–alcohol-dependent brothers. Thus, the increased risk of developing marijuana dependence was in part independent of the familial risk of developing alcohol dependence.

A comparable risk was seen with cocaine dependence, ie, having a sibling with alcohol dependence and comorbid cocaine dependence increased a person's risk of developing cocaine dependence independent from the risk of developing alcohol dependence. A similar pattern was seen with habitual smoking.

Siblings share many characteristics that may be risk factors for the development of substance dependence, and so the familial association between proband depen-

Table 3. Lifetime Rates of Marijuana Dependence, Cocaine Dependence, and Habitual Smoking in COGA Siblings*

	Alcohol-Dependent Siblings		Non–Alcohol-Dependent Siblings	
COGA Proband	**Male**	**Female**	**Male**	**Female**
Lifetime Rates of Marijuana Dependence in COGA Siblings				
Marijuana dependent,% (No.†)				
Yes	56.7 (300)	42.8 (180)	15.2 (302)	7.7 (558)
No	31.5 (295)	16.2 (191)	10.7 (300)	4.8 (629)
χ^2_1	38.1	31.6	2.8	4.4
P	<.001	<.001	<.10	<.05
Lifetime Rates of Cocaine Dependence in COGA Siblings				
Cocaine dependent,% (No.†)				
Yes	43.3 (293)	40.5 (195)	13.7 (293)	8.8 (593)
No	18.9 (302)	18.2 (176)	5.5 (309)	2.0 (594)
χ^2_1	41.7	22.0	11.7	26.5
P	<.001	<.001	<.001	<.001
Lifetime Rates of Habitual Smoking in COGA Siblings				
Habitual smoking,% (No.†)				
Yes	61.3 (380)	60.7 (229)	35.7 (356)	29.9 (708)
No	40.9 (215)	37.3 (142)	20.3 (246)	14.6 (479)
χ^2_1	23.0	19.2	16.5	37.1
P	<.001	<.001	<.001	<.001

*Comparison of rates of marijuana dependence, cocaine dependence, or habitual smoking given proband diagnosis, and separated by the presence or absence of alcohol dependence in siblings and sex. COGA indicates Collaborative Study on the Genetics of Alcoholism.

†Total number of siblings in the group.

©1998 American Medical Association. All rights reserved.

Downloaded From: http://archpsyc.jamanetwork.com/ on 03/06/2015

Table 4. Risk of Developing Substance Dependence in Siblings, Proportional Hazards Model*

	Risk Ratio (95% Confidence Interval)		
	Marijuana Dependence (n = 3007)	Cocaine Dependence (n = 3006)	Habitual Smoking (n = 3009)
Sibling characteristics			
Birth cohort			
Born before 1950	1.00	1.00	1.00
Born 1950-1959	3.50 (2.09-5.86)†	5.70 (1.65-12.24)†	0.63 (0.53-0.77)†
Born 1960 or later	6.68 (4.05-11.01)†	9.47 (4.07-22.00)†	0.50 (0.41-0.61)†
Sex			
Male	1.00	1.00	1.00
Female	0.52 (0.43-0.62)†	0.96 (0.76-1.21)	0.86 (0.75-0.98)‡
Habitual smoking	1.56 (1.28-1.89)†	1.47 (1.14-1.89)†	NA
Alcohol dependence	2.67 (2.16-3.31)†	2.71 (2.07-3.55)†	2.06 (1.78-2.39)†
Marijuana dependence	NA	4.21 (3.27-5.43)†	1.45 (1.22-1.72)†
Cocaine dependence	3.40 (2.77-4.19)†	NA	1.40 (1.15-1.71)†
Proband characteristics			
Sex			
Male	1.00	1.00	1.00
Female	1.16 (0.95-1.42)	1.24 (0.95-1.62)	1.09 (0.91-1.30)
Habitual smoking	0.96 (0.80-1.16)	0.83 (0.65-1.07)	**1.77 (1.48-2.12)**†
Alcohol dependence	2.13 (1.05-4.29)‡	1.61 (0.00-2178.00)	1.66 (0.99-2.79)
Marijuana dependence	**1.78 (1.45-2.18)**†	1.05 (0.79-1.39)	1.09 (0.93-1.29)
Cocaine dependence	0.93 (0.76-1.15)	**1.71 (1.29-2.27)**†	1.08 (0.90-1.30)

*Both the Collaborative Study on the Genetics of Alcoholism and control siblings were used in these multivariate analyses. NA indicates not applicable; boldface, findings discussed in "Results" section.

†P<.001.

‡P<.01.

dence and sibling dependence may be related to these factors. For example, geographic center, race, and birth cohort may contribute to a familial clustering of substance dependence. We next analyzed the onset of substance dependence in all siblings (COGA and control) by means of the Cox proportional hazards model to evaluate the effect of multiple, potentially confounding characteristics of probands and siblings. Race and center of assessment were controlled for in these analyses. Results of the Cox proportional hazards model as applied to the onset of marijuana dependence, cocaine dependence, and habitual smoking in siblings are presented in **Table 4**.

The strongest predictor variables for the onset of any substance dependence were the sibling's own characteristics, ie, birth cohort and comorbid substance dependence. Sibling's sex was a predictor in the development of marijuana dependence and habitual smoking but did not influence the rate of cocaine dependence. Also, proband sex did not influence the risk of developing marijuana dependence, cocaine dependence, or habitual smoking.

After controlling for these predictor variables, ie, sibling's birth cohort, sex, and comorbid substance dependence, the presence of marijuana and alcohol dependence in probands significantly predicted the onset of marijuana dependence in siblings, whereas cocaine dependence and habitual smoking in probands did not (Table 4).

As with marijuana dependence, the strongest predictors for the onset of cocaine dependence were characteristics of the siblings: birth cohort and other substance-dependence diagnoses (in this case, alcohol dependence, marijuana dependence, and habitual smoking). After controlling for these predictor variables, cocaine dependence in probands significantly predicted the onset of cocaine dependence in siblings, whereas marijuana dependence and habitual smoking in probands did not. Alcohol dependence in probands gave an elevated risk ratio (1.6) for the development of cocaine dependence; however, the confidence interval with bootstrapping was wide (0-2178) and did not reach statistical significance. This was because of the low prevalence of cocaine dependence in control subjects.

Analysis of the specificity of the familial transmission of substance dependence was extended to habitual smoking. As with the other dependence diagnoses, characteristics of the siblings, (ie, siblings' alcohol, marijuana, and cocaine dependence) were strong predictors of the onset of habitual smoking. Birth cohort was also a significant predictor, with younger cohorts being at lower risk for developing habitual smoking. After controlling for these predictor variables, habitual smoking in probands significantly predicted the onset of habitual smoking in siblings, whereas marijuana and cocaine dependence in probands did not. There was a trend for alcohol dependence in probands to increase the risk of habitual smoking in siblings; however, this did not reach statistical significance.

Access to marijuana and cocaine may influence the increased rate of drug dependence in siblings, since probands with comorbid drug dependence may supply these drugs to their siblings. Siblings of probands with comorbid marijuana dependence were more likely to have used marijuana than siblings of probands without marijuana dependence (81.2% vs 66.2%; $\chi^2_1 = 79.4$; $P<.001$). Similarly, siblings of probands with comorbid cocaine dependence were more likely to have used cocaine than siblings of probands without cocaine dependence (50.4% vs 30.0%; $\chi^2_1 = 118.5$; $P<.001$). To minimize this "availability" bias, we repeated the analyses using only sib-

©1998 American Medical Association. All rights reserved.
Downloaded From: http://archpsyc.jamanetwork.com/ on 03/06/2015

lings who had ever used marijuana for marijuana analyses and only those who had ever used cocaine for the cocaine analyses. Restricting analyses to siblings who had used marijuana and cocaine did not diminish the familial specificity of substance dependence, and there was little change in the risk ratio (marijuana: RR, 1.8 for all siblings vs 1.7 for siblings who used marijuana; cocaine: RR, 1.7 for all siblings vs 1.6 for siblings who used cocaine).

COMMENT

Although studies support the familial transmission of alcohol and substance dependence, individuals are frequently dependent on multiple substances, raising the possibility of a general addictive tendency. By examining the most common substances on which subjects from the COGA were dependent—alcohol, marijuana, cocaine, and habitual smoking—we sought to clarify the familial relationship between them.

The first aim was to examine the influence of comorbid substance dependence in alcohol-dependent probands on the rate of developing alcohol dependence in their siblings. A lifetime diagnosis of alcohol dependence was present in half of the brothers and one quarter of the sisters of alcohol-dependent subjects. Regardless of the presence or absence of comorbid substance dependence, rates of alcohol dependence in siblings were stable. This result was not consistent with a continuum model of severity of addiction influencing the familial clustering of alcoholism, since one would have expected a more severe form of addiction in probands (alcohol and comorbid drug dependence) to confer a greater risk to siblings for the development of alcohol dependence compared with a less severe form of addiction in probands (alcohol dependence only).

The second aim of these analyses was to evaluate the risk of developing marijuana dependence, cocaine dependence, and habitual smoking in siblings of alcohol-dependent probands. The risk for developing these disorders was elevated in siblings with and without alcohol dependence, and was related to the presence of substance dependence in the probands. Thus, the increased risk of developing substance dependence was in part independent of the familial transmission of alcoholism.

Finally, there was substance-specific familial transmission of dependence even after many associated variables that may result in association of dependence among siblings were taken into account. Marijuana dependence in probands specifically increased the risk of marijuana dependence in siblings, and cocaine dependence in probands specifically increased the risk of cocaine dependence in siblings. An analysis of habitual smoking, a proxy for tobacco dependence, also found a specific familial pattern. Substance dependence in individuals did not result in a general increase in all forms of dependence in their siblings, but instead resulted in a substance-specific increase in dependence. This result was consistent with previous studies[9-13] that did not support a model of only a "general addictive tendency" for all forms of addiction.

In addition to these substance-specific transmission factors, these analyses supported a common risk factor for dependence that was transmitted in families. Alcohol dependence in probands increased the risk of developing all substance dependence we studied, independent of the risk of developing alcohol dependence.

The familial transmission of substance dependence may result from genetic and/or environmental factors, and 1 environmental factor that may mediate the specificity of substance dependence was examined. Siblings of substance-dependent probands may have greater access to illicit substances and, therefore, more opportunity to develop drug dependence. To examine this possibility, analyses were restricted to those siblings who had ever used marijuana or cocaine. Among those who had used marijuana, siblings of marijuana-dependent probands still had elevated rates of marijuana dependence compared with siblings of non–marijuana-dependent probands. There was a similar finding with cocaine dependence. Thus, the specificity of the familial aggregation of marijuana and cocaine dependence remained after the analyses were restricted to those persons who used these illicit drugs.

Another possible confounding variable of these results was the presence of antisocial personality disorder (ASPD), since alcohol dependence, drug dependence, and ASPD are all frequently comorbid. Reanalyzing the data after removing all probands with ASPD (22.6% of COGA probands and 0.9% of control probands), and then all probands with ASPD and siblings (7.0% of COGA siblings and 3.2% of control siblings) gave essentially the same results. Thus, this specificity of the familial aggregation of substance dependence was not explained by ASPD.

This study also demonstrated that many factors increase a person's risk for developing substance dependence. The risk for developing marijuana or cocaine dependence was greatly increased by an individual's own characteristics: comorbid substance dependence, birth cohort, and sex. A diagnosis of substance dependence was the strongest predictive factor for the development of other substance dependence, ie, alcohol dependence, cocaine dependence, and habitual smoking greatly increased the risk of developing marijuana dependence, and alcohol dependence, marijuana dependence, and habitual smoking greatly increased the risk of developing cocaine dependence.

Birth cohort and sex also influenced the risk of developing dependence. Consistent with general population studies,[4,27] there were significant secular trends in the development of substance dependence. Younger age groups, even though they had a shorter time to develop substance dependence, were at much higher risk for developing alcohol, marijuana, and cocaine dependence. This may reflect the increased availability and acceptability of these substances. Conversely, younger age groups were at lower risk of becoming habitual smokers. Finally, sex influenced the risk of developing both alcohol and marijuana dependence, with men more likely than women to be afflicted with these disorders. However, cocaine dependence did not show this usual sex difference after controlling for other covariates.

These are several strengths of this study. Analyses were based on a large sample that permitted the study of the familial transmission of specific substance dependence. Further, data were obtained via personal interviews of all subjects, which have been shown to be considerably more sensitive than family history reports in detecting an affected individual.[28] Finally, strict diagnostic criteria were used, and

©1998 American Medical Association. All rights reserved.
Downloaded From: http://archpsyc.jamanetwork.com/ on 03/06/2015

individuals were considered substance dependent only if they met *DSM-III-R* criteria by their own report.

A limitation of this study was the relative lack of probands with a diagnosis of drug dependence and no alcohol dependence. Though more than 200 control probands were selected, there were only 6 control probands with marijuana or cocaine dependence and no alcohol dependence. As a result, we were unable to analyze the impact of drug dependence alone on the familial transmission of alcohol and substance dependence. Another limitation was that alcohol-dependent probands were recruited from treatment settings; as a result, these results may not be representative of families of untreated alcohol-dependent individuals. Finally, all data were based on retrospective self-reports.

In conclusion, alcohol and substance dependence frequently co-occur within individuals and aggregate within families. Having a sibling with alcohol dependence increases an individual's risk of developing alcohol dependence, but the risk is not further changed by a sibling's comorbid substance dependence. Marijuana dependence, cocaine dependence, and habitual smoking cluster within families, and this clustering is substance specific and, in part, independent of the clustering of alcohol dependence in families. These data are consistent with both common and specific addictive risks that are transmitted in families. This specificity suggests that independent causative factors may be involved in the development of each type of substance dependence.

Accepted for publication June 30, 1998.

This national collaborative study was supported by the National Institute on Alcohol Abuse and Alcoholism (NIAAA), Bethesda, Md, through Public Health Service grants NIAAA U10AA08401, U10AA08402, and U10AA08403. This work was also supported by Public Health Services grants AA00231 and MH14677.

Presented in part at the Annual Meeting of the Research Society on Alcoholism, Steamboat Springs, Colo, June 1995.

We would like to acknowledge the thoughtful suggestions of the Collaborative Study on the Genetics of Alcoholism publication committee in the preparation of this article. The assistance of Shen Lu in data analysis and Barbara Rothwell in manuscript preparation were greatly appreciated. We also valued the suggestions of Tony Hinrichs, PhD, and Joseph Mullaney, MA.

The Collaborative Study on the Genetics of Alcoholism (Henri Begleiter, MD, State University of New York, Health Sciences Center at Brooklyn, Brooklyn, NY, principal investigator; Theodore Reich, MD, Washington University, St Louis, Mo, co–principal investigator) includes 6 centers where data collection takes place. The 6 sites and principal investigator and coinvestigators are as follows: Indiana University, Indianapolis (John I. Nurnberger, Jr, MD, PhD; Ting-Kai Li, MD; P. Michael Conneally, PhD; Howard J. Edenberg, PhD); University of Iowa, Iowa City (Raymond Crowe, MD; Samuel Kuperman, MD); University of California at San Diego and Scripps Institute, San Diego, Calif (Marc Schuckit, MD; Floyd Bloom, MD); University of Connecticut (Victor Hesselbrock, PhD); State University of New York Health Sciences Center at Brooklyn (Henri Begleiter, MD; Bernice Porjesz, PhD); and Washington University (Theodore Reich, MD; C. Robert Cloninger, MD; John Rice, PhD).

Reprints: Laura Jean Bierut, MD, Department of Psychiatry, Washington University School of Medicine, 4940 Children's Pl, St Louis, MO 63110 (e-mail: laura@newhar.wustl.edu).

REFERENCES

1. Winokur G, Reich T, Rimmer J, Pitts FN Jr. Alcoholism, III: diagnosis and familial psychiatric illness in 259 alcoholic probands. *Arch Gen Psychiatry*. 1970;23:104-111.
2. Schuckit MA, Goodwin DA, Winokur G. A study of alcoholism in half-siblings. *Am J Psychiatry*. 1972;128:1132-1136.
3. Guze SB, Cloninger CR, Martin R, Clayton PJ. Alcoholism as a medical disorder. *Compr Psychiatry*. 1986;27:501-510.
4. Reich T, Cloninger CR, Van Eerdewegh P, Rice JP, Mullaney J. Secular trends in the familial transmission of alcoholism. *Alcohol Clin Exp Res*. 1988;12:458-464.
5. Goodwin DW, Schulsinger F, Hermansen L, Guze SB, Winokur G. Alcohol problems in adoptees raised apart from alcoholic biological parents. *Arch Gen Psychiatry*. 1973;28:238-243.
6. Cloninger CR, Bohman M, Sigvardsson S. Inheritance of alcohol abuse: cross-fostering analysis of adopted men. *Arch Gen Psychiatry*. 1981;38:861-868.
7. Hrubec Z, Omenn GS. Evidence of genetic predisposition to alcoholic cirrhosis and psychosis: twin concordances for alcoholism and its biological end points by zygosity among male veterans. *Alcohol Clin Exp Res*. 1981;5:207-215.
8. Kendler KS, Heath AC, Neale MC, Kessler RC, Eaves LJ. A population-based twin study of alcoholism in women. *JAMA*. 1992;268:1877-1882.
9. Hill SY, Cloninger CR, Ayre AB. Independent familial transmission of alcoholism and opiate abuse. *Alcohol Clin Exp Res*. 1977;1:335-342.
10. Meller WH, Rinehart R, Cadoret RJ, Troughton E. Specific familial transmission in substance abuse. *Int J Addict*. 1988;23:1029-1039.
11. Mirin SM, Weiss RD, Griffin ML, Michael JL. Psychopathology in drug abusers and their families. *Compr Psychiatry*. 1991;32:36-51.
12. Rounsaville BJ, Kosten TR, Weissman MM, Prosoff B, Pauls D, Anton SF, Merikangas K. Psychiatric disorders in relatives of probands with opiate addiction. *Arch Gen Psychiatry*. 1991;48:33-42.
13. Luthar SS, Rounsaville BJ. Substance misuse and comorbid psychopathology in a high-risk group: a study of siblings of cocaine misusers. *Int J Addict*. 1993;28:415-434.
14. 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.
15. Cadoret RJ, Yates WR, Troughton E, Woodworth G, Stewart MA. Adoption study demonstrating two genetic pathways to drug abuse. *Arch Gen Psychiatry*. 1995;52:42-52.
16. Pickens RW, Svikis DS, McGue M, Lykken DT, Heston LL, Clayton PJ. Heterogeneity in the inheritance of alcoholism: a study of male and female twins. *Arch Gen Psychiatry*. 1991;48:19-28.
17. Tsuang MT, Lyons MJ, Eisen SA, Goldberg J, True W, Lin N, Meyer JM, Toomey R, Farone SV, Eaves L. Genetic influences on *DSM-III-R* drug abuse and dependence: a study of 3,372 twin pairs. *Am J Med Genet*. 1996;67:473-477.
18. Kessler RC, Crum RM, Warner LA, Nelson CB, Schulenberg J, Anthony JC. Lifetime co-occurrence of *DSM-III-R* alcohol abuse and dependence with other psychiatric disorders in the National Comorbidity Survey. *Arch Gen Psychiatry*. 1997;54:313-321.
19. Helzer JE, Pryzbeck TR. The co-occurrence of alcoholism with other psychiatric disorders in the general population and its impact on treatment. *J Stud Alcohol*. 1988;49:219-224.
20. Swan GE, Carmelli D, Cardon LR. Heavy consumption of cigarettes, alcohol and coffee in male twins. *J Stud Alcohol*. 1997;58:182-190.
21. Nurnberger JI Jr, Bucholz KK, Crowe R, Hesselbrock VM, Reich T, Schmidt I, Schuckit MA, van Eerdewegh P, Begleiter H. Systematic ascertainment of families with multiple cases of alcoholism for the Collaborative Study of the Genetics of Alcoholism (COGA) [abstract]. *Alcohol Clin Exp Res*. 1995;19(2):72a.
22. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised*. Washington, DC: American Psychiatric Association; 1987.
23. Feighner JP, Robins E, Guze SB, Woodruff RA Jr, Winokur G, Munoz R. Diagnostic criteria for use in psychiatric research. *Arch Gen Psychiatry*. 1972;26:57-63.
24. Bucholz KK, Cadoret R, Cloninger CR, Dinwiddie SH, Hesselbrock VM, Nurnberger 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.
25. Cox D. Regression models and life tables. *J R Stat Soc Br*. 1972;34:187-220.
26. Effron B, Tibshirani R. Bootstrap methods for standard errors, confidence intervals, and other measures of accuracy. *Stat Sci*. 1986;1:421-429.
27. Robins LN, Helzer JE, Weissman MM, Orvaschel H, Gruenberg E, Burke JD Jr, Regier DA. Lifetime prevalence of specific psychiatric disorders in three sites. *Arch Gen Psychiatry*. 1984;41:949-958.
28. Andreasen NC, Rice J, Endicott J, Reich T, Coryell W. The family history approach to diagnosis: how useful is it? *Arch Gen Psychiatry*. 1986;43:421-429.

©1998 American Medical Association. All rights reserved.

Downloaded From: http://archpsyc.jamanetwork.com/ on 03/06/2015

systems of working memory in schizophrenia. *Schizophr Res.* 1997;27:1-10.
9. Fleming K, Goldberg TE, Binks S, Randolph C, Gold JM, Weinberger DR. Visuospatial working memory in patients with schizophrenia. *Biol Psychiatry.* 1997; 41:43-49.
10. Gold JM, Carpenter C, Randolph C, Goldberg TE, Weinberger DR. Auditory working memory and Wisconsin Card Sorting Test performance in schizophrenia. *Arch Gen Psychiatry.* 1997;54:159-165.
11. Wexler BE, Stevens AA, Bowers AA, Sernyak MJ, Goldman-Rakic P. Word and tone working memory deficits in schizophrenia. *Arch Gen Psychiatry.* 1998;55: 1093-1096.
12. Goldman-Rakic PS, Selemon LD. Functional and anatomical aspects of prefrontal pathology in schizophrenia. *Schizophr Bull.* 1997;23:437-458.
13. Goldman-Rakic PS, Scalaidhe SP, Chafee MV. Domain specificity in cognitive systems. In: Gazzaniga MS, ed. *The New Cognitive Neurosciences.* 2nd ed. Cambridge, Mass: MIT Press; 2000:733-742.
14. Goldman-Rakic PS. The physiological approach: functional architecture of working memory and disordered cognition in schizophrenia. *Biol Psychiatry.* 1999; 46:650-661.
15. Smith EE, Jonides J. Neuroimaging analyses of human working memory. *Proc Natl Acad Sci U S A.* 1998;95:12061-12068.
16. Cabeza R, Nyberg L. Imaging cognition, II: an empirical review of 275 PET and fMRI studies. *J Cogn Neurosci.* 2000;12:1-47.
17. Mishkin M, Ungerleider LG, Macko KA. Object vision and spatial vision: two cortical pathways. *Trends Neurosci.* 1983;6:414-417.
18. Kohler S, Kapur S, Moscovitch M, Winocur G, Houle S. Dissociation of pathways for object and spatial vision: a PET study in humans. *Neuroreport.* 1995; 6:1865-1868.
19. Haxby JV, Grady CL, Horwitz B, Ungerleider LG, Mishkin M, Carson RE, Herscovitch P, Schapiro MB, Rapoport SI. Dissociation of object and spatial visual processing pathways in human extrastriate cortex. *Proc Natl Acad Sci U S A.* 1991;88:1621-1625.
20. McIntosh AR, Grady CL, Ungerleider LG, Haxby JV, Rapoport SI, Horwitz B. Network analysis of cortical visual pathways mapped with PET. *J Neurosci.* 1994; 14:655-666.
21. Wilson FA, Scalaidhe SP, Goldman-Rakic PS. Dissociation of object and spatial processing domains in primate prefrontal cortex. *Science.* 1993;260:1955-1958.
22. Ungerleider LG, Courtney SM, Haxby JV. A neural system for human visual working memory. *Proc Natl Acad Sci U S A.* 1998;95:883-890.
23. Courtney SM, Petit L, Haxby JV, Ungerleider LG. The role of prefrontal cortex in working memory: examining the contents of consciousness. *Philos Trans R Soc Lond B Biol Sci.* 1998;353:1819-1828.
24. Owen AM. The functional organization of working memory processes within human lateral frontal cortex: the contribution of functional neuroimaging. *Eur J Neurosci.* 1997;9:1329-1339.
25. Park S, Holzman PS. Association of working memory deficit and eye tracking dysfunction in schizophrenia. *Schizophr Res.* 1993;11:55-61.
26. Park S, Puschel J, Sauter BH, Rentsch M, Hell D. Spatial working memory deficits and clinical symptoms in schizophrenia: a 4-month follow-up study. *Biol Psychiatry.* 1999;46:392-400.
27. Park S, Holzman PS, Goldman-Rakic PS. Spatial working memory deficits in the relatives of schizophrenic patients. *Arch Gen Psychiatry.* 1995;52:821-828.
28. Keefe RS, Roitman SE, Harvey PD, Blum CS, DuPre RL, Prieto DM, Davidson M, Davis KL. A pen-and-paper human analogue of a monkey prefrontal cortex activation task: spatial working memory in patients with schizophrenia. *Schizophr Res.* 1995;17:25-33.
29. Barch DM, Carter CS, Braver TS, Sabb FW, MacDonald A III, Noll DC, Cohen JD. Selective deficits in prefrontal cortex function in medication-naive patients with schizophrenia. *Arch Gen Psychiatry.* 2001;58:280-288.
30. Farmer CM, O'Donnell BF, Niznikiewicz MA, Voglmaier MM, McCarley RW, Shenton ME. Visual perception and working memory in schizotypal personality disorder. *Am J Psychiatry.* 2000;157:781-788.
31. Roitman SE, Mitropoulou V, Keefe RS, Silverman JM, Serby M, Harvey PD, Reynolds Mohs RC, Siever LJ. Visuospatial working memory in schizotypal personality disorder patients. *Schizophr Res.* 2000;41:447-455.
32. Javitt DC, Strous RD, Grochowski S, Ritter W, Cowan N. Impaired precision, but normal retention, of auditory sensory ("echoic") memory information in schizophrenia. *J Abnorm Psychol.* 1997;106:315-324.
33. Javitt DC, Liederman E, Cienfuegos A, Shelley AM. Panmodal processing imprecision as a basis for dysfunction of transient memory storage systems in schizophrenia. *Schizophr Bull.* 1999;25:763-775.
34. Stevens AA, Donegan NH, Anderson M, Goldman-Rakic PS, Wexler BE. Verbal processing deficits in schizophrenia. *J Abnorm Psychol.* 2000;109:461-471.
35. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition.* Washington, DC: American Psychiatric Association; 1994.
36. Weiner E. Clinical outcomes in a research clinic population vs a CMHC population. *Schizophr Res.* 1999;36(suppl 1-3):350-351.
37. First MB, Spitzer RL, Gibbon M, Williams JBW. *Structured Clinical Interview for* DSM-IV *Axis 1 Disorders, Version 2.0, 8/98 Revision.* New York: New York State Psychiatric Institute; 1998.
38. Overall JE, Gorham DR. The Brief Psychiatric Rating Scale. *Psychol Rep.* 1962; 10:799-812.
39. Andreasen NC. Negative symptoms in schizophrenia: definition and reliability. *Arch Gen Psychiatry.* 1982;39:784-788.
40. Smith EE, Jonides J, Koeppe RA, Awh E, Schumacher EH, Minoshima S. Spatial vs object working memory: PET investigations. *J Cogn Neurosci.* 1995;7:337-356.
41. Postle BR, Jonides J, Smith EE, Corkin S, Growdon JH. Spatial, but not object, delayed response is impaired in early Parkinson's disease. *Neuropsychology.* 1997; 11:171-179.
42. Vanderplas JM, Garvin EA. The association value of random shapes. *J Exp Psychol.* 1959;57:147-154.
43. Garcia-Perez MA. Forced-choice staircases with fixed step sizes: asymptotic and small-sample properties. *Vision Res.* 1998;38:1861-1881.
44. Cnaan A, Laird NM, Slasor P. Using the general linear mixed model to analyse unbalanced repeated measures and longitudinal data. *Stat Med.* 1997;16:2349-2380.
45. Braff DL. Information processing and attention dysfunctions in schizophrenia. *Schizophr Bull.* 1993;19:233-259.
46. Green MF, Nuechterlein KH, Mintz J. Backward masking in schizophrenia and mania, I: specifying a mechanism. *Arch Gen Psychiatry.* 1994;51:939-944.
47. O'Donnell BF, Swearer JM, Smith LT, Nestor PG, Shenton ME, McCarley RW. Visual perception and recognition in schizophrenia. *Am J Psychiatry.* 1996;153: 687-692.
48. O'Donnell BF, Farmer CM, Swearer JM, Nizniliewicz MA, Nestor PG, Shenton ME, McCarley RW. Visual information processing in schizophrenia and schizotypal personality disorder [abstract]. In: Program and abstracts of the annual meeting of the Society for Neuroscience; October 23-28, 1999; Miami, Fla. Abstract 14.9.
49. Cadenhead KS, Serper Y, Braff DL. Transient vs sustained visual channels in the visual backward masking deficits of schizophrenia patients. *Biol Psychiatry.* 1998; 43:132-138.
50. Braff DL, Saccuzzo DP. Information processing dysfunction in paranoid schizophrenia: a two-factor deficit. *Am J Psychiatry.* 1981;138:1051-1056.
51. Schwartz BD, Evans WJ, Sautter F, Winstead DK. Schizophrenic feature recognition deficits are independent of task criterion. *Schizophr Res.* 1992;7:185-189.
52. Cadenhead KS, Geyer MA, Butler RW, Perry W, Sprock J, Braff DL. Information processing deficits of schizophrenia patients: relationship to clinical ratings, gender and medication status. *Schizophr Res.* 1997;28:51-62.
53. Snitz BE, Curtis CE, Zald DH, Katsanis J, Iacono WG. Neuropsychological and oculomotor correlates of spatial working memory performance in schizophrenia patients and controls. *Schizophr Res.* 1999;38:37-50.
54. Owen AM, Beksinska M, James M, Leigh PN, Summers BA, Marsden CD, Quinn NP, Sahakian BJ, Robbins TW. Visuospatial memory deficits at different stages of Parkinson's disease. *Neuropsychologia.* 1993;31:627-644.
55. Castner SA, Williams GV, Goldman-Rakic PS. Reversal of antipsychotic-induced working memory deficits by short-term dopamine D_1 receptor stimulation. *Science.* 2000;287:2020-2022.

Correction

Error in Byline. In the article titled "Familial Transmission of Substance Dependence: Alcohol, Marijuana, Cocaine, and Habitual Smoking" (*Arch Gen Psychiatry*. 1998;55:982-988), the third author, Henri Begleiter, MD, should have been listed as Henri Begleiter, PhD. The ARCHIVES regrets the error.

©2002 American Medical Association. All rights reserved.
Downloaded From: http://archpsyc.jamanetwork.com/ on 03/06/2015