Genetic-Environmental Interaction in the Genesis of Aggressivity and Conduct Disorders

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Background: The purpose of this study was to determine the effect of an adverse adoptive home environment on adoptee conduct disorder, adult antisocial behavior, and two measures of aggressivity, all of which are behaviors that contribute to adult antisocial personality disorder and that also are associated with increased vulnerability to drug abuse and/or dependence.

Methods: The study used an adoption paradigm in which adopted offspring who were separated at birth from biologic parents with documented (by prison and hospital records) antisocial personality disorder and/or alcohol abuse or dependence were followed up as adults. They and their adoptive parents were interviewed in person. These adoptees were compared with controls whose biologic background was negative for documented psychopathologic behavior. Subjects were 95 male and 102 female adoptees and their adoptive parents.

Results: Multiple regression analysis was used to measure separately genetic and environmental effects. It showed that (1) a biologic background of antisocial personality disorder predicted increased adolescent aggressivity, conduct disorder, and adult antisocial behaviors, and (2) adverse adoptive home environment (defined as adoptive parents who had marital problems, were divorced, were separated, or had anxiety conditions, depression, substance abuse and/or dependence, or legal problems) independently predicted increased adult antisocial behaviors. Adverse adoptive home environment interacted with biologic background of antisocial personality disorder to result in significantly increased aggressivity and conduct disorder in adoptees in the presence of but not in the absence of a biologic background of antisocial personality disorder.

Conclusions: Environmental effects and genetic-environmental interaction account for significant variability in adoptee aggressivity, conduct disorder, and adult antisocial behavior and have important implications for the prevention and intervention of conduct disorder and associated conditions such as substance abuse and aggressivity.

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A number of studies have suggested that genetic factors interacting with the environment are etiologic in the genesis of childhood and adolescent conduct disorder and adult antisocial personality disorder. Recently, Cadoret and colleagues demonstrated that, in both male and female adoptees, conduct disorder and aggressivity acted as important intervening variables in the relation between biologic parents with antisocial personality disorder and adoptee outcome for drug abuse and/or dependence (Cadoret et al. and R.J.C., W.R.Y., E.T., C. Cutrona, PhD, G.W., M.A.S., unpublished data, 1995). These studies showed evidence of two genetic factors leading to drug abuse. One factor, from alcoholic biologic parentage, correlated directly with drug abuse; the second factor, from biologic parents with antisocial personality disorder, led to conduct disorder, adolescent aggressivity, and then to adult antisocial personality disorder and drug abuse. It is this second genetic factor and its relationship to conduct disorder, aggressivity, and antisocial personality disorder that will be addressed in this article.

In both male and female adoptees, environmental variables defined by a variety of psychiatric and other problems in adoptive parents (alcoholism, anxiety conditions, depression, and marital problems, including separation

See Methods on next page
METHODS

Details of the methods are available in Cadoret et al.© This section outlines the essentials of the methods only.

SUBJECT SELECTION

Subjects for this study were recruited from four adoption agencies: Lutheran Social Services of Iowa, Des Moines; Catholic Charities of the Archdiocese of Dubuque (Iowa), Hillcrest Family Services, Cedar Rapids, Iowa; and the Iowa Department of Human Services, Des Moines. Adoptees and their adoptive parents were selected on the basis of whether the adoptee had a biologic parent with alcohol or other drug abuse and/or dependence or antisocial personality disorder (experimental group) or whether there was no evidence from available records of biologic parent psychopathologic conditions (control group). Controls were matched to patients in the experimental group by agency, sex, age, and age of the biologic mother at the time of the adoptee's birth. All adoptees in the study had to have been separated at birth or within a few days from the biologic parent, placed with nonrelatives, and eventually adopted successfully by nonrelatives. Adoptees were further selected to be between 18 and 47 years of age at the time of the study.

Adoptive parents were initially contacted by the agency that handled the adoption. If these parents agreed to be contacted by the investigators, a research assistant explained the project and obtained written permission from both the adoptive parents and the adoptee to participate in the study. The contact procedure and permission request were designed to protect the confidentiality of adoptive families and were approved by the Human Subjects Internal Review Board of the University of Iowa College of Medicine, Iowa City.

DIAGNOSIS OF BIOLOGIC PARENTS

A method was devised to locate hospital and prison records of biologic parents in such a way that the names of parents were not revealed. Many institutional records did not contain enough information to make a diagnosis of antisocial personality disorder or substance abuse and/or dependence, eg, an emergency department visit for acute gastroenteritis. In those cases, subjects were not used in the study. Only when a diagnosis was made was that subject used in the study. Diagnoses were made as follows: institutional records were read independently by three psychiatrists (R.J.C., W.R.Y., and M.A.S.), and psychiatric diagnoses were made according to DSM-III-R® criteria. The x statistics for diagnoses of substance abuse and antisocial personality disorder were satisfactory and ranged from 0.66 to 0.84 for biologic parent alcohol abuse and/or dependence and from 0.67 to 0.79 for antisocial personality disorder. Disagreements about diagnoses were settled by conference between the three judges. When agreement was not possible, these cases were discarded and not used in the study.

SUBJECT ATTRITION AND SELECTION BIAS

The overall refusal rate was 54%. There was no evidence that biologic parent status (control or experimental) was correlated with refusal.© The final sample consisted of 95 male and 102 female adoptees.

STUDY INSTRUMENTS AND THEIR ADMINISTRATION

All interviews were administered in person by a research assistant who was blind to the biologic background of the adoptee. The adoptive parent interview was administered to adoptive parents to gather information about adoptee physical health, temperament, development, and school achievement from infancy to adulthood. The interview also inquired into substance use and/or abuse in family members. Because the previous adoption study of Cadoret et al._6 found correlations between drug abuse and family disturbances such as separations, divorce, and psychiatric problems, the adoptee and adoptive parent interviews sought evidence of such problems as well as emotional or psychiatric problems in the adoptive household members, including the exposure of the adoptee to these situations. To further specify adoptive parent psychiatric problems, each parent was administered the Diagnostic Interview Schedule Screening Interview by computer. This screening instrument was used to minimize time commitments from subjects yet allow a psychiatric diagnosis to be made on the basis of a structured, self-administered instrument. Robins and Marcus© have shown sensitivities for diagnoses between the Diagnostic Interview Schedule Screening Interview and the NIMH Diagnostic Interview Schedule, Version III, Revised.© Diagnoses such as alcohol abuse, drug abuse, and antisocial personality disorder have sensitivities of greater than 95%. Only two diagnoses had sensitivities less than 75%: cognitive impairment and somatization disorder. Remaining diagnoses such as depression had intermediate sensitivities.

Adoptees received the NIMH Diagnostic Interview Schedule, Version III, Revised described by Robins et al.© Additional demographic data was collected from adoptees as well as information about the adoptive environment, including behavior or psychiatric problems in sibs and parents.

DIAGNOSIS OF ADOPTEE OUTCOME

DSM-III-R criteria were used to characterize adoptee psychiatric outcome. Aggressivity in the adoptee was measured by a scale devised by Loney et al.© An additional five items were added to this scale.© Aggressivity was measured by the sum of these items. Adolescent conduct disorder was defined by the sum of endorsed items from Robins,2 such as truancy, school expulsion, lying, and stealing. These items from Robins had been used in the DSM-III© as criteria that had to occur prior to age 15 years to make an adult diagnosis of antisocial personality disorder. Four adoptee outcome variables were used for this study to characterize the conduct disorder path. These were defined as follows: (1) childhood aggression, the sum of 16 items from the parent interview detailing aggressive behaviors during the preschool and grade school years; (2) adolescent aggressivity, the sum of the items in the modified scale from Loney et al.© described above; (3) conduct disorder, the sum of the items from Robins' described above; and (4) adult antisocial behavior, the sum of DSM-III adult behavior criterion items for the diagnosis of antisocial personality disorder.
ASSESSMENT OF ENVIRONMENTAL FACTORS

Both sources of information, the parent interview and the adoptee interview, were used to determine the presence of a substance abuse problem or an anxiety or depression diagnosis in adoptive parents or siblings. The presence of a marital problem, including divorce or separation, or serious physical health problems in family members was also determined from the adoptee and adoptive parent interviews.

Diagnosis of potentially adverse adoptive parent conditions made from interviews, including the Diagnostic Interview Schedule Screening Interview, included such factors as anxiety conditions (phobias, general anxiety disorder, panic disorder, and agoraphobia), depression, marital problems (including separation and divorce), legal problems, and alcohol and other drug problems. Adverse adoptive home environment factor was equivalent to the total number of the following conditions that were met: presence of a marital problem in adoptive parents; divorce or separation of adoptive parents; alcohol or other drug abuse and/or dependence in a parent; depression in a parent; anxiety condition in a parent (eg, panic disorder and generalized anxiety disorder); other psychopathologic condition in a parent (eg, conduct disorder and somatization); and legal problems in a parent.

The distribution of this composite variable is shown in Table 1. This is the same variable that was found to predict adult antisocial personality disorder as a main effect in log-linear analyses in this sample.4

STATISTICAL METHODS

The purpose of this study was to examine more closely for genetic-environmental interaction the conduct disorder pathway between a biologic parent with antisocial personality disorder and adoptee outcome variables (conduct disorder and aggressivity), which lead to substance abuse and adult antisocial personality disorder. The original analysis had used log-linear methods to construct models. To focus on the conduct disorder path and to have more power to detect interaction by using ordinal or interval variables, a series of linear multiple regression models was developed to assess the influence of genetic factors, environmental factors, and their interactions.

The basic multiple regression model started with biologic variables of parent with antisocial personality disorder (X1) or alcoholism (X2) as independent variables. There were 21 alcoholic biologic mothers in the data who had a record of drinking during the pregnancy of adoptees in this study. Thus, the environmental factor of drinking during pregnancy was confounded with biologic parent alcoholism. To control for this confound, a separate independent variable was added to model 1 as X3, biologic mother who used alcohol during adoptee pregnancy. Four measures of adoptee outcome (aggressivity as a child, aggressivity as an adolescent, conduct disorder, and adult antisocial behavior) were included as dependent variables (Y1 to Y4), resulting in model 1:

\[ Y_1 = C + B_1X_1 + B_2X_2 + B_3X_3, \]

where C represents a constant, and B, the regression coefficient.

From model 1, the importance of the genetic factors (including the antenatal exposure to alcohol, which was largely confounded with alcoholism in biologic mothers) could be determined as measured by the R² of the model. The second step involved adding environmental factors to model 1. Accordingly, the composite variable of the adverse adoptive home environment conditions (E) was added to the basic model, resulting in model 2:

\[ Y_2 = C + B_1X_1 + B_2X_2 + B_3X_3 + B_4E, \]

Environmental effects were assessed both by differences in R² or proportion of variance accounted for in the dependent variables by the addition of the environmental variable and by the significance level of the individual regression coefficient of the environmental variable.

Another measure of environmental effect is the genetic-environmental interaction, or the change in manifestation of an environmental factor determined by the presence or absence of a genetic factor. To assess genetic-environmental interaction, three additional terms were added to model 2, consisting of cross products of each genetic factor with the environmental factor (X1 × E, X2 × E, and X3 × E) resulting in model 3:

\[ Y_3 = C + B_1X_1 + B_2X_2 + B_3X_3 + B_4E + B_5(X_1 × E) + B_6(X_2 × E) + B_7(X_3 × E), \]

where B1 through B7 are regression coefficients associated with the interaction terms. Again, the R² of each of these models can be compared with the corresponding R² from model 2 to assess the significance of adding the terms measuring interaction.

Regression analysis was used to assess the significance of the fit of each model, to determine the significance of each separate term's contribution to the model, to determine the improvement in fit from one model to another, and to determine the effect of sex of adoptee on the four outcome measures. Probability for individual terms in each model were computed on the basis that each variable was the last to be entered into the model. In this way, the presence of all other factors in the model was controlled.

and divorce) increased the probability of development of adoptee conduct disorder as well as a related condition, adoptee aggressivity (Cadoret et al⁴ and R.J.C., W.R.Y., E.T., C. Cutrona, PhD, G.W., M.A.S., unpublished data, 1995). This effect was independent of the genetic influence of biologic parents with alcoholism or antisocial personality disorder. The finding of significant environmental factors influencing adoptee conduct disorder and aggressivity in the pathway from biologic parent with antisocial personality disorder to adoptee drug abuse and/or dependence raised the question of the role of genetic-environmental interaction as an additional factor. This interaction is the focus of this article.

Literature from previous adoption studies indicates that the genetic-environmental interaction is of importance in the genesis of antisocial behavior. Relevant to the present study are the findings from three independent earlier adoption studies.⁵ Two of these studies showed a genetic-environmental interaction between a
genetic background of alcoholic and/or antisocial behaviors and an adverse adoptive home environment (defined as a psychiatric or behavioral problem in adoptive parent or sibling or adoptive parents who experience marital separation or divorce). The nature of the interaction was such that an adverse adoptive home environment in the presence of a genetic factor contributed by a parent with alcoholism and/or antisocial personality disorder produced a much higher number of adolescent conduct disorder symptoms than would be predicted by either genetic or environmental factors acting independently. The third study showed a significant interaction between adoptee age at the time of adoptive placement and a genetic background of alcoholism and/or antisocial personality disorder. Later age at placement in the adoptive home in the presence of the genetic diathesis for alcoholism and/or antisocial personality disorder resulted in a significant increase in conduct disorder behaviors in adolescence.

A later adoption study from a different agency also showed a significant genetic-environmental interaction between genetic diatheses for alcoholism and/or antisocial personality disorder and psychiatric or alcohol problems in the adoptive family for adoptee conduct disorder behaviors. Again the adverse adoptive home environment produced a much higher number of conduct behaviors in the presence of the genetic diathesis.

Thus, at least four independent adoption studies have demonstrated a significant genetic-environmental interaction in the genesis of adolescent conduct disorder behavior. One of the studies has suggested sex differences in the genetic and environmental factors important to conduct disorder, but these studies characterized the biologic parents only through adoption agency records, which did not allow an unequivocal diagnosis of biologic backgrounds such as alcoholism or antisocial personality disorder. Only one of the studies used prison records of biologic parents and was able to thereby diagnose antisocial personality disorder. That study showed the interaction between a parent with antisocial personality disorder and the adverse adoptive home environment variable described above.

The present study was able to use hospital and prison records of biologic parents to diagnose substance abuse and antisocial personality disorder. Adoptive home environment was better characterized by the use of multiple informants and by the administration of a structured psychiatric interview to the adoptive parents. This article will describe the evidence for genetic-environmental interaction found between biologic factors of antisocial personality disorder and alcoholism and adverse home environment in the genesis of conduct disorder, aggressivity, and adult antisocial behaviors, which contribute to vulnerability to drug and alcohol abuse and to adult antisocial personality disorder.

### RESULTS

A regression analysis fitting the three models using the total data set of male and female adoptees showed that there were no significant male-female differences in genetic, environmental, or genetic-environmental interaction effects. In this analysis, a sex term, sex by genetics, sex by environment, and a triple interaction term, sex by genetics by environment, were included in the model tested. None of the added interaction terms were significant. The sex term was significant, as would be expected, because men generally rate higher on aggressivity, conduct disorder, and antisocial behavior. However, inclusion of a sex term in models involving the total sample did not change the estimate of the significance of the individual terms (genetic, environmental, and genetic-environmental) in the models, and, in the analyses that follow, results are presented for the total sample across sex of adoptee.

Linear regression was used on untransformed dependent variables for these analyses. Examination of the dependent variables showed a J-shaped distribution for each, with the modal value at zero, a distribution commonly found with psychopathologic variables. This intrinsic skewing cannot be transformed to normality, but the regressions were rerun using logarithmic transformation, $\log (Y + 1)$; the logarithmic-logarithmic transformation, $\log \log (Y + 1) + 1$; and the inverse transformation, $-1/(Y + 1)$, and the same pattern of significant interactions occurred. As an additional check, the models were fit using ordinal logistic regression, and, in this analysis, the pattern of significant interaction was the same as the linear regression analyses with untransformed variables. Although transformation of the dependent variable in some cases may reduce or eliminate mild interactions, it typically has little effect on strong interactions, so that it is not at all paradoxical that the same interactions may appear under several transformations of the dependent variable. Accordingly, we will present the linear regression analyses with untransformed variables herein.

### Table 2

<table>
<thead>
<tr>
<th>Table 2. Distribution of Count for the Variable Adverse Adoptive Home Environment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse Factors Present, No.</td>
</tr>
<tr>
<td>0</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>2</td>
</tr>
<tr>
<td>3</td>
</tr>
<tr>
<td>4</td>
</tr>
<tr>
<td>5</td>
</tr>
<tr>
<td>6</td>
</tr>
</tbody>
</table>

See also pages 895, 900, 906, and 925.
ing a biologic mother who was known to drink alcohol during her pregnancy (Table 2) and conduct disorder and adult antisocial behavior. The direction of the effect is for maternal drinking during pregnancy to be associated with an increase in these types of behaviors as indicated by the positive regression coefficients shown in Table 2.

Table 3 presents the results of fitting model 2 to the four behavioral outcomes variables. The main feature shown by the R² values is a general improvement in fit accomplished through the addition of the environmental factor of adoptive homes with adverse parental conditions. This is shown graphically in Figure 1. Two of the four models show a significant improvement in dependent variable prediction: conduct disorder and adult antisocial behavior. The direction of effect, as shown in Table 3 (last column), is for increased amount of psychopathologic conditions to be associated with an increased number of adverse adoptive home environment factors. Thus, the results support the conclusion of a significant environmental effect, which was demonstrated by the log-linear modeling (Cadoret et al. and R.J.C., W.R.Y., E.T., C. Cutrona, PhD, G.W., M.A.S., unpublished data, 1995). The next step in the analysis was to add genetic-environmental interaction terms to model 2.

Table 4 shows the results of adding the three genetic-environmental interaction terms to model 2. Three of the four genetic-environmental interaction terms for biologic parent with antisocial personality disorder by adverse adoptive home environment are significant ( "X×E" column), and overall, the addition of genetic-environmental interaction terms increases R² significantly for the same three dependent variables: childhood aggressivity, adolescent aggressivity, and conduct disorder (Figure 1). The nature of these interactions is clarified by Figure 2 through Figure 4, in which the interaction is graphed by plotting predicted outcome, eg, aggressivity, against increasing adverse adoptive home environment factors for adoptees with and without a biologic background of a parent with antisocial personality disorder. All three figures show that in the absence of a biologic parent with antisocial personality disorder, there is no correlation between adoptee outcome and adverse adoptive home environment (broken line, Figures 2 through 4). In contrast, the adverse adoptive home environment–outcome relationship is significant only for adoptees with a biologic parent with antisocial personality disorder (solid line, Figures 2 through 4).

The findings of genetic-environmental interaction in these studies confirm the importance of such interactions in the genesis of conduct disorder and aggressivity. Adult antisocial behavior does not show the genetic-environmental effect demonstrated by aggression and conduct disorder (Table 4) but does show a main effect for environment, the adverse adoptive home environment factor. The lack of genetic-environmental interaction is also apparent from the R²'s of the three models predicting adult antisocial behavior (Figure 1). Reasons for failure to demonstrate a role for the genetic-environmental interaction in adult antisocial behaviors are not apparent. There are many possible explanations, such as other environmental (or genetic) factors operating in early adulthood to modify the conduct disorder trajectory. For example, the finding in these data that prenatal exposure to alcohol was a factor in significantly increasing adult antisocial symptoms (Tables 1 through 3) demonstrates the operation of other factors modifying adult behavior.

The variable of adverse adoptive home environment is similar to that of previous studies detailed in the intro-

### Table 2: Genetic-Environmental Factors in Behavior Disorder Pathway to Drug Abuse: Model 1*

<table>
<thead>
<tr>
<th>Dependent Variable</th>
<th>R²</th>
<th>Alcoholic Biologic Parent (X₁)</th>
<th>Biologic Parent With Antisocial Personality Disorder (X₂)</th>
<th>Prenatal Alcohol Exposure (X₃)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Childhood aggressivity</td>
<td>.02</td>
<td>−.01</td>
<td>.15</td>
<td>.02</td>
</tr>
<tr>
<td>Adolescent aggressivity</td>
<td>.09†</td>
<td>.05</td>
<td>.26</td>
<td>.06</td>
</tr>
<tr>
<td>Conduct disorder</td>
<td>.07§</td>
<td>0</td>
<td>.19</td>
<td>.15</td>
</tr>
<tr>
<td>Adult antisocial behavior</td>
<td>.10‡</td>
<td>.01</td>
<td>.10</td>
<td>.28</td>
</tr>
</tbody>
</table>

*Values are R² values (column 1) and standardized regression coefficients (columns 2 through 4).
†Significant at P= .10.
‡Significant at P= .01.
§Significant at P= .001.

### Table 3: Genetic-Environmental Factors in Behavior Disorder Pathway to Drug Abuse: Model 2*

<table>
<thead>
<tr>
<th>Dependent Variable</th>
<th>R²</th>
<th>Alcoholic Biologic Parent (X₁)</th>
<th>Biologic Parent With Antisocial Personality Disorder (X₂)</th>
<th>Prenatal Alcohol Exposure (X₃)</th>
<th>Adverse Adoptive Home Environment (E)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Childhood aggressivity</td>
<td>.04</td>
<td>−.04</td>
<td>.16</td>
<td>.01</td>
<td>.14‡</td>
</tr>
<tr>
<td>Adolescent aggressivity</td>
<td>.13§</td>
<td>.01</td>
<td>.28</td>
<td>.05</td>
<td>.19§</td>
</tr>
<tr>
<td>Conduct disorder</td>
<td>.13§</td>
<td>.04</td>
<td>.22</td>
<td>.12§</td>
<td>.25§</td>
</tr>
<tr>
<td>Adult antisocial behavior</td>
<td>.15§</td>
<td>−.03</td>
<td>.13</td>
<td>.26§</td>
<td>.23§</td>
</tr>
</tbody>
</table>

*Values are R² values (column 1) and standardized regression coefficients (columns 2 through 5).
†Significant at P= .05.
‡Significant at P= .01.
§Significant at P= .10.
‖Significant at P= .001.
In this study, it was possible to specify the genetic background more exactly through the use of prison and hospital records and to separate the genetic factors associated with alcohol abuse from those contributing to antisocial personality disorder. The results herein show that it is the genetic diathesis for antisocial personality disorder, not that for alcoholism, that interacts with the adverse adoptive home environment to produce a significant increase in conduct disorder and aggression in adoptees. A previous independent adoption study by Crowe16 found a similar interaction between biologic parent with antisocial personality disorder (diagnosed by prison records) and adverse adoptive home environment (reviewed in Cadoret et al4). In the remaining previously studied samples reported by Cadoret et al,5,18 interaction was reported in both men and women and for the combination of biologic backgrounds of alcohol and of antisocial personality disorder. However, in those studies, biologic parent diagnosis was determined from adoption agency records only, so there is more uncertainty as to the validity of the distinction in those studies between genetic diatheses for alcoholism and antisocial personality disorder.

In the log-linear models that were fit to these data (Cadoret et al4 and R.J.C., W.R.Y., E.T., C. Cutrona, PhD, G.W., M.A.S., unpublished data, 1995), no evidence of genetic-environmental interaction was found. In part, this failure to detect interactions in the log-linear modeling reflects the fact that information is lost in the formation of dichotomous variables in the log-linear situation. In the linear regression models herein, both the dependent variables and the adverse home environment factor were used in their full range of values, thus providing more information and increased power to detect interaction.

In two of the studies described in the introduction,15,16 there was evidence for an environmental effect of adoptee age at the time of adoptive home placement on adolescent conduct disorder: adoptees who were older at placement showed more conduct disorder symptoms during adolescence. In one of these studies (reviewed in Cadoret et al5), there was a significant genetic-environmental interaction, with biologic parent with alcoholism and/or antisocial personality disorder and age of placement reflecting in an increased number of conduct disorder behaviors. In the present study, no environmental or genetic-environmental effect was found involving age of adoptee at placement in the adoptive home. Reasons for this failure at replication are not clear.

Many variables affect the variability of age at placement. For example, in the early studies reported by Cadoret and Cain,6,17 more adoptees were adopted after hav-
ing spent their first 6 months in foster care or in home management homes on a college campus where they were cared for by a number of undergraduate students enrolled in a home economics course. This experience was associated with several behavioral manifestations later in life: increased affective symptoms\textsuperscript{12} and increased conduct disorder symptoms.\textsuperscript{9} Adoptees in the present study were not involved in the home management situation, and more were placed directly with adoptive families, thus bypassing foster care and later placement and generally resulting in earlier placement.

One of the factors in the model that showed a significant effect on outcome (Tables 2 through 4, “Prenatal Alcohol Exposure” column) is having a biologic mother who was drinking while pregnant with the proband adoptee. There were 21 of these mothers in the sample, most of whom also had diagnoses of alcohol abuse and/or dependence. Thus, the observed effect could be environmental (due to alcohol intake during pregnancy or some other associated adverse factor such as smoking, poor diet, or use of other drugs) or could be considered a genetic-environmental interaction. It is not likely to represent a purely genetic factor because alcoholic biologic parents did not produce this effect in their offspring when controlling for maternal drinking (Tables 2 through 4). In support of the effect being related to maternal drinking during pregnancy (or other variables such as associated smoking, other drug use, and poor nutrition) is the fact that the offspring of these 21 drinking mothers had significantly lower birth weights than the remaining sample of adoptees.\textsuperscript{4} The results suggest that prenatal exposure to alcohol could represent an additional vulnerability to adult antisocial behavior and ultimately to drug abuse and/or dependence in offspring.

One interpretation of the adoptee outcomes—adverse adoptive home environment correlation would suggest that aggressive, conduct disorder behaviors in adoptees causes increased parental distress, which would manifest as a higher number of adverse home environment factors. This interpretation, however, is inconsistent with the findings that show that the score distribution of the adverse home environment factor is the same when comparing families with adoptees from backgrounds of antisocial personality disorder with those families whose adoptees do not have a parent with antisocial personality disorder. This similarity of score distribution is shown in Table 5. There is no evidence that biologic parents with antisocial personality disorder caused an increase in the number of adverse adoptive home environment factors. This finding is also an argument against a selective placement hypothesis, which would claim that children from a biologic background of antisocial personality disorder are more likely to be placed into more disturbed families. Figures 2 through 4 show that in the absence of a biologic background of antisocial personality disorder, there is essentially a zero slope relating the number of adverse home environment factors and aggressivity or conduct dis-

\begin{table}[h!]
\centering
\begin{tabular}{|c|c|c|}
\hline
\textbf{Score} & \textbf{Antisocial Personality Disorder Background} & \\
\hline
0 & Yes & 15 (27) \ 43 (30.3) \\
1 & Yes & 17 (31) \ 37 (26.1) \\
2 & Yes & 14 (26) \ 27 (19.0) \\
3 & Yes & 4 (7) \ 19 (13.4) \\
4 & Yes & 4 (7) \ 9 (6.3) \\
5 & Yes & 0 \ 5 (3.5) \\
6 & Yes & 1 (2) \ 2 (1.4) \\
\hline
\end{tabular}
\caption{Score Distribution for Adverse Adoptive Home Environment in Adoptees With and Without a Background of Antisocial Personality Disorder}
\end{table}

\*Values are No. (%) of adoptees. Percentages are based on column totals.
order. This is compatible with a direction of effect from parent to adoptee rather than adoptee to parent. Thus, the evidence from the genetic-environmental interaction data is consistent with the interpretation that the adverse home environment factors result in increased aggressive and conduct disorder behaviors in the presence of a biologic background of antisocial personality disorder.

The environmental effects and their interaction reported herein are important for the prevention of conduct disorders, aggressivity, and associated substance abuse. The interaction results show that antisocial behaviors and aggressivity are increased in the presence of predisposing genetic factors. These adverse environments are ubiquitous but are likely to be especially increased in families of persons with antisocial personality disorder, where marital problems and substance abuse are extremely common.\(^1\)\(^-\)\(^3\) The environment in the present study as defined by adverse home environment factors is undoubtedly less extreme than would be the case for individuals exposed to parents with antisocial personality disorder. We would predict more marked environmental effects in that situation. These considerations would lead to action to protect genetically predisposed individuals from these adverse environments. In child psychiatry, aggressivity and conduct disorder combine in the clinical entity of the unsocialized aggressive child.\(^8\) Aggressivity has been shown to lead to less improvement in children with conduct disorder.\(^9\) The present finding relating both aggressivity and conduct disorder to a biologic background of antisocial personality disorder is compatible with findings from family studies associating aggressive conduct disorder with parents with antisocial personality disorder.\(^20\)

In addition to aggressive conduct disorder, behaviors of aggressivity and conduct disorder are of special importance in predicting drug abuse.\(^21\)-\(^23\) Childhood and adolescent aggression have been implicated as risk factors in the transition from moderate to heavy use of drugs\(^24\) and in the transition both from no drug use to drug use and from drug use to abuse.\(^25\) There is suggestive evidence that aggressivity predicts substance abuse independently of such variables as hyperactivity,\(^26\)-\(^27\) and conduct disorder.\(^28\) Conduct disorder is well documented as a factor in drug abuse and/or dependence in both men and women.\(^28\)-\(^30\) The present adoption study is compatible with the role of aggressivity and conduct disorder in substance abuse described above but reports for the first time to our knowledge the importance of both genetic and environmental factors acting in an interactive fashion, so that the environmental factor depends on the presence of a particular genetic background for its effect. The adverse home environment factor described herein as interacting with the biologic background of antisocial personality disorder could have influenced the adoptee through such influences as altered parental affection, availability, and involvement, which are parental behaviors that have been reported to have an effect on both aggressivity and drug use.\(^31\) The present data would suggest that such parental effects act through genetic-environmental interaction.

Examples of genetic-environmental interaction rarely have been described in human behavior and may just reflect the fact that very few adoption studies are available to measure such effects directly. One study of adopted offspring of criminal parents did look at the effect of criminal adoptive parents on criminality and was unable to find evidence for a genetic-environmental interaction,\(^32\) although there was evidence for genetic transmission of criminality. However, a recent adoption study of schizophrenia from Finland has reported a genetic-environmental interaction: disturbed adoptive families were more likely to produce disturbed adoptees if the latter were offspring of schizophrenic mothers.\(^33\) Subjects with a genetic predisposition for schizophrenia appeared to be more vulnerable to a disturbed adoptive family environment, an interaction similar to the type described herein with conduct disorder and aggressivity.

Genetic-environmental interaction has also been reported in a previous Iowa adoption study. Cutrona et al\(^34\) reported an interaction between family conflict and adoptive family psychopathologic conditions and a biologic background of alcoholism. Among women with at least one alcoholic biologic parent, the presence of conflict (reported by the adoptive parents) or adoptive family psychopathologic conditions increased the chance of adoptee alcohol abuse and/or dependence. No evidence for similar interactions were found for men.

In a similar vein, there is little direct evidence in the literature for genetic inheritance of aggressivity. A recent review of 12 published twin studies of aggressiveness showed that eight were consistent with a genetic effect.\(^35\) An additional twin study from Iowa found a significant heritability in both boys (78%) and girls (36%) for aggressivity.\(^36\) While, to our knowledge, no adoption study relates aggressiveness in biologic parents to aggressiveness in offspring, one study that correlated psychiatric disorders in adoptive and biologic parents of adoptees with aggressive conduct disorder in children found a significant increase of biologic fathers with antisocial personality disorder among the biologic parents of the adoptees with conduct disorder.\(^37\) This result is compatible with the present data and suggests inheritance of aggressiveness from a parent with antisocial personality disorder because antisocial personality disorder is associated with increased aggressivity.\(^38\)

The finding of nonadditive effects as shown in Figures 2 through 4 for aggressivity and conduct disorder raises the question of what genetic mechanism could account for these results. Kendler and Eaves\(^39\) present three major models for the joint effect of genes and environment on the liability to psychiatric illness. Their first model of simple additivity of genetic and environmental factors is rejected by these findings. Their second model is compatible with these data and proposes a genetic control of sensitivity to effects of the environment. The third model proposed by Kendler and Eaves is not compatible with these data. This third model proposes that there is genetic control of an individual’s exposure to the environment as, for example, an individual whose personality traits lead him or her to experience stressful events, which in turn precipitate psychiatric illness. In the present situation, adoptees are not in a position to seek out disturbed parents, who occur with equal frequency in adoptees from control as well as alcoholic biologic backgrounds. It appears that the differential sensitivity model is closer to the present facts.

Knowledge that genetic-environmental interaction is
important in aggressivity and conduct disorder could be of importance in the current efforts to link human behaviors with biologic factors in molecular genetics. In these studies, efforts are made to correlate behavioral outcome with the presence of certain genomes. Interaction effects could be important in the analysis of genetic association studies in which correlations are sought between clinical conditions and the presence of a particular allele of a candidate gene or in linkage studies or other genetic analyses such as segregation analyses.** Thus, the interaction findings of this study are of relevance to both basic science, eg, in correlating behavior with molecular genetic factors, and applied social science, for example, in determining high-risk populations that are especially vulnerable to common environmental factors, such as adverse parenting, for the purpose of intervention and prevention. Awareness that genetic-environmental interaction occurs with such common conditions as described in this article should also lead to important changes in mathematical models used in behavior genetics, which sometimes assume that there is no genetic-environmental interaction to simplify model fitting.

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